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# OPIUM ADDICTION

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# OPIUM ADDICTION

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PHILADELPHIA

*From the Narcotic Wards of the Philadelphia General Hospital*

Expenses of this research were defrayed by the Committee on Drug Addiction, New York City. The research was carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction, in the wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

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# FOREWORD

The Philadelphia Committee for the Clinical Study of Opium Addiction herewith presents a series of papers containing the results of investigations undertaken at its suggestion and carried on under its supervision on the general subject of opium addiction in man. These pages, with the exception of this statement and the General Summary, are reprinted from the *Archives of Internal Medicine,* volumes 43 and 44, and the Committee is indebted to this journal for the opportunity to collect them in this form. This Committee was organized in 1925 at the request of the Committee on Drug Addictions of New York and has been enabled to carry on its work by means of subsidies from this Committee.

The Committee has conducted this study along clinical and chemical lines and has not entered the field of the social aspect of the abuse of the so-called vicious drugs. The work was carried on for the most part in the Narcotic Wards and Laboratory of the Philadelphia General Hospital. Assistance was received from various members of the Staff of the Department of Pharmacology of the University of Pennsylvania. From the Pennsylvania Hospital for Mental Diseases there came some useful data relative to the use of narcotics by those of a higher economic status. Working with the Committee have been an internist, a clinical pathologist, a psychologist, a psychiatrist and a clinical chemist, and it has from time to time consulted with other specialists who were able to give valuable advice and information bearing on this study.

The unusual clinical facilities at the Philadelphia Hospital were of great use to the Committee, 861 patients having been observed during the three year period comprising the study. In addition to the positive findings, there are important negative findings which the Committee feels are scarcely less valuable.

The Committee acknowledges its obligation and gratitude to Dr. Charles E. Terry, Executive of the Committee on Drug Addictions of New York City, and to the interested and generous individuals for whom he has acted. The thanks of the Committee are also due Dr. Arthur B. Light, Internist in Charge, and to his corps of workers whom he so efficiently directed during the course of the study.

The thanks of the Committee are also herewith extended to Dr. Alfred N. Richards of the University of Pennsylvania, member of the New York Committee on Drug Addictions, for his collaboration and for certain facilities of his laboratory which were placed at the disposal of the Philadelphia Committee.

Dr. Joseph C. Doane, Chairman
Dr. J. Harold Austin
Dr. Earl D. Bond
Dr. Robert G. Torrey
Dr. Theodore H. Weisenburg
Dr. Horatio C. Wood, Jr.

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# I. THE CONDUCT OF THE ADDICT IN RELATION TO INVESTIGATIVE STUDY

The data to be presented in a series of papers, of which this is the first, have been obtained from studies of persons addicted to opium or its derivatives who have applied for treatment at the Narcotic Wards of the Philadelphia General Hospital. These wards are maintained by the city of Philadelphia and have no relationship to law enforcement agencies. In this introductory paper, we wish to present our impressions of the behavior of the addict for the purpose of emphasizing the existence of obstacles which, if not fully appreciated, may result in failure of investigative efforts. A detailed report of the psychiatric and psychologic studies will be published later by members of the staff investigating this phase of the problem of opium addiction.

## REASONS FOR SEEKING TREATMENT

The person who presents himself for treatment in these wards does so of his own volition and for one or more of the following reasons: He is disgusted with his slavery to the drug; he desires temporary refuge from the police, or for financial reasons he wishes to reduce the amount of his daily dosage or to obtain free maintenance for a time. Regardless of the motive for seeking treatment, patients who apply for admission either have had an unusually large dosage (as they express it, are well "shot-up") or are manifesting early withdrawal symptoms. In either event, they will agree to any sort of experimentation as long as it promises their immediate or early acceptance for treatment. This apparent desire on their part to cooperate must not be taken seriously, as we will point out later.

## RELATIONSHIP TO DRUGS

After a person has become firmly addicted to the use of opium or one of its derivatives, we have reason to believe that the problem of securing and maintaining an adequate supply of the drug comes to be the major purpose of his existence. To an extraordinary degree, he develops a sagacity and persistence in this direction which may outmatch the abilities of those who are conducting the investigation. The ingenuity that is displayed in maintaining channels of supply is amazing. We have come to believe that practically every word which the addict utters and every deed which he may perform are based directly or indirectly on a motive concerned with the maintenance of

these channels of supply. He will plead with or threaten those about him who are in a position to supply him with the drug. Whatever method he may use has been previously determined by careful consideration on his part as to which may be the more successful.

Undoubtedly there are some who desire to give up the drug on account of disgust and give this reason in all sincerity. The patients encountered in the wards of the Philadelphia General Hospital are practically all from the so-called underworld. A considerable number of them have, however, at one time lived in better circumstances. Not any of them has fallen so low as to fail to realize that he is an outlaw under present conditions of the law and public opinion. This realization together with the undoubted tax on their mental processes levied by the very ingenuity which these persons display is enough to bring about this so-called disgust with the drug. This feeling, however, quickly vanishes when the addict is confronted with the sufferings attendant on failure of supply of his drug.

### GENERAL BEHAVIOR IN THE WARD

After admission to the ward with the knowledge that the drug is available and will be supplied for certain lengths of time, the addict becomes amenable. His behavior is excellent, and he desires to cooperate in any experiment which does not interfere with his daily dosage. This cooperative attitude on the part of the addict is real and sincere but lasts only as long as the effects of the drug persist, usually a matter of hours. When the effects of the drug pass off, all the sagacity and ingenuity on his part are brought into play as only those who have been associated with this type of person can appreciate.

Not only must the observer forstall the schemes which the addict is devising to obtain the drug, but he must defeat plans, made before admission, for the restoration of his supply should his craving become unbearable. He may have attempted to bring the drug into the ward concealed in his clothing, letters, jewelry or in any orifice of the body large enough to hold it. Extreme care must be taken to search the addict before admission. We have found drugs concealed in the soiled dressings covering abscesses resulting from infections caused by hypodermic injections.

Should his attempts to bring a certain quantity of the drug into the ward have failed, he resorts to plans devised to obtain it from friends outside of the hospital, or he schemes with fellow addicts who are about to be discharged and who have signified their intentions to him of immediately returning to the use of the drug. He will attempt to bribe any one who appears open to temptation. Letters will come addressed to

him which have been written on paper previously saturated with the drug, dried, ironed out and then inscribed with a harmless message. He will extract the drug by either chewing the paper or redissolving it in water. Sometimes the drug is concealed under the stamp of the envelop. The wooden stem of a match changed into a cylinder has been found to contain a drug. He will accuse or betray his best friend in order that he may gain favor from those in charge. Telegrams and telephone messages will arrive bringing the news of the death of a member of the family, asking his immediate return home. These are but a few of the methods employed to obtain drugs, and unless forestalled they will ruin any studies made during the withdrawal period. In addition, there is always danger that the patient may be aided by a fellow addict who may have drugs in his possession, or by a drug pedler who will furnish drugs without charge when it insures him the return of the addict with funds in the near future.

Practically 80 per cent of the addicts appearing for treatment were using heroin before admission to the wards. The rest were addicted to morphine, except one or two who used camphorated tincture of opium and tincture of opium. In the cases of morphine and heroin addiction, the hypodermic method of administration was the choice, except in several cases of sniffing and in two in which self-intravenous administration was employed. After admission to the ward, all persons used for study were supplied with drugs in the form of morphine administered hypodermically. Enough of the drug was given to allay any possible suffering. We find that morphine easily displaces heroin in maintaining comfort and rest. All studies to be reported must be considered as studies made during morphine addiction and morphine withdrawal.

While the person is under the influence of the narcotic, his behavior is normal. Not having much to do, he spends his time smoking cigarets and engaging in conversations, chiefly on drug addiction. As a rule, the addict is interested in sporting events and the latest newspaper scandals. Although supplied with fiction of the lighter variety, he is not a consistent reader while in the ward. He eats well, sleeps well and helps to keep the ward clean, lending a helping hand to any kind of work requested. He is docile, well behaved and is altogether easy to deal with while receiving the drug and while desiring to remain in the ward.

### WITHDRAWAL SYMPTOMS

The withdrawal of the drug results in a striking change in the appearance and behavior of such a person. The symptoms which make their appearance have frequently been described in the literature

(Johnson,[1] Levinstein,[2] Sollier,[3] Morat,[4] Bishop[5] and Lambert[6]). Having studied their onset carefully, we shall describe them briefly in the order of their appearance as we have observed them.

As the time approaches for what would have been the addict's next administration of the drug, one notices that he glances frequently in the direction of the clock and manifests a certain degree of restlessness. If the administration is omitted, he begins to move about in a rather aimless way, failing to remain in one position long. He is either in bed, sitting in a chair, standing up or walking about, constantly changing from one to another. With this restlessness, yawning soon appears, which becomes more and more violent. At the end of a period of about eight hours, restlessness becomes marked. He will throw himself onto a bed, curl up and wrap the blankets tightly around his shoulders, sometimes burying his head in the pillows. For a few minutes he will toss from side to side and then suddenly jump out of the bed and start to walk back and forth, head bowed, shoulders stooping. This lasts only a few minutes. He may then lie on the floor close to the radiator, trying to keep warm. Even here he is not contented, and he either resumes his pacing about or again throws himself onto the bed, wrapping himself under heavy blankets. At the same time he complains bitterly of suffering with cold and then hot flashes, but mostly chills.

He breathes like a person who is cold, in short, jerky, powerful respirations. His skin shows the characteristic pilomotor activity well known to these persons by the name of "cold turkey." The similarity of the appearance of the skin at this stage to that of a plucked turkey is striking. Coincident with this feeling of chilliness, he complains of being unable to breathe through his nose. Nasal secretion is excessive. He has a most abject appearance, but is fairly docile in his behavior. This is a picture of his appearance during the first eight hours.

Often at the end of this period, the addict may become extremely drowsy and unable to keep his eyes open. If he falls asleep, which is often the case, he falls into a deep slumber well known as the "yen" sleep. It takes unusual noises to awaken him. The sleep may last for as long as eight or twelve hours. On awakening, he is more restless

1. Communication from G. H. Smith, Esq., to Dr. Johnson, Lancet **1**:707, 1841-1842.

2. Levinstein, E.: Die Morphiumsucht, 1878, p. 14.

3. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine med., 1894, p. 146.

4. Morat, D.: Le sang et les secretions au cours de la morphinomanie et de la desintoxication, These de Paris, 1911.

5. Bishop, E. S.: Narcotic Addiction: A Systemic Disease Condition, J. A. M. A. **60**:431 (Feb. 8) 1913.

6. Lambert, A.: Nelson's Looseleaf Medicine, 1920, vol. 2, p. 607A.

than ever. Lacrimation, yawning, sneezing and chilliness are extreme. A feeling of suffocation in the back of the throat is frequently mentioned. Usually at this stage, the addict complains of cramps, locating them most frequently in the abdomen, but often in the back and lower extremities. A right rectus rigidity with pain localized over the appendical region is not uncommon; one can easily be misled in the diagnosis, since at this stage a leukocytosis is frequently present, as will be pointed out in a later paper. Vomiting and diarrhea appear. He may vomit large quantities of bile-stained fluid. Perspiration is excessive. The underwear and pajamas may become saturated with sweat. Muscular twitchings are commonly present; they may occur anywhere, but are most violent in the lower extremities. He may sit in bed with his leg flexed, grasping it tightly below the knee, fearing the twitch which will suddenly throw it into complete extension and which he cannot control. If he is handed a cigaret to smoke, his hand trembles so violently that he may have difficulty in placing it in his mouth. The tremor is so marked that he is unable to light it himself.

He refuses all food and water, and frequently sleep is unknown from this point. It is at this stage that he may one minute beg for a "shot" and in the next minute threaten physical violence. Nothing can make him smile. He will beat his head against the wall or throw himself violently on the floor. Any behavior which he thinks may bring about the administration of the drug will be resorted to. Occasionally he may complain of diplopia. Seminal emissions in the male and orgasms in the female frequently occur.

We believe that the height of these withdrawal symptoms is reached somewhere between the period of forty-eight and seventy-two hours following the last dose of the drug taken. The readministration of the drug promptly brings about a dramatic change. The patient becomes exceedingly docile almost simultaneously with the puncture of the hypodermic needle. In a few minutes he begins to feel warm, and the gooseflesh and perspiration are no longer visible. He speaks about a "heaviness" in his stomach, but regards this as a welcome symptom presaging relief. In a period ranging from thirty minutes to one hour, the muscular tremors disappear. He has become strong and well. He no longer walks with bowed head and stooped shoulders. He stands erect, is quite cheerful and lights his cigaret like any normal person. He becomes profuse in his apologies for his conduct during the abrupt withdrawal of the drug.

The intensity of some of these symptoms is undoubtedly subject to control on the part of the patient. We have stated that his mode of behavior is governed largely by his attempts to impress his suffering on those observing him. On the other hand, if there is a possible chance of obtaining his liberty from the ward he will state, though feeling ill,

that he "feels fine," "has an excellent appetite" and is "sleeping well." He may have been successful in smuggling and administering the drug to himself and yet feign withdrawal symptoms so as to allay suspicion. When it is time for his discharge, he may feel well from the effects of the drug that he has been able to obtain through smuggling.

### UNRELIABILITY IN RELATIONSHIP TO STUDY

This control of his symptoms on the part of the patient must be thoroughly understood by those engaged in the employment of various sorts of treatment. We believe that in many cases false conclusions are drawn as to the efficacy of a treatment if the value is deduced from the statements of the patient and his appearance. The scopolamine treatment that we have employed has always been stated by the patient who has been previously treated and who wishes to enter the ward to be "the best he has ever undergone, all others being torture." When he is just recovering from the effects of the scopolamine, it is "the worst," all others being excellent. When the time approaches for his discharge and he is anxious to obtain his liberty, the treatment again becomes the most successful he has ever had; he appears to have fully recovered his normal strength when he may still be so weak that he may not be able to walk several blocks without collapsing.

### CONCLUSIONS

We have attempted in this paper to give a picture of the opium addict as we have found him in the wards of the Philadelphia General Hospital. We believe this description to be essential so far as it points out the difficulties encountered in the study of human addicts. Without this introductory paper, the reader might fail to appreciate in the papers which are to follow, the deceptiveness of the addict during experimentation.

## II. PHYSICAL CHARACTERISTICS AND PHYSICAL FITNESS OF ADDICTS DURING ADMINISTRATION OF MORPHINE

Among the many problems present in connection with opium addiction is one about which there seems to be a good deal of controversy—Does addiction to this drug bring about physical deterioration? A good deal of confusion that exists in the literature on this subject is due, as Terry and Pellens [1] have pointed out, to variation in individual susceptibility and the amount of daily dosage and to the failure to distinguish between drug balance and early withdrawal symptoms.

Opium addicts, when once "hooked," as they so aptly express their plight, need a certain daily dosage to prevent the appearance of "withdrawal symptoms." In certain types of users, this dosage may remain constant in small quantities for years. Another and far more numerous group is composed of those who increase the amount used until eventually they are forced to undergo treatment or begin reduction of the dose themselves. In either event, they must endure some or all of the withdrawal symptoms, which are practically always associated with loss of weight and, according to the addict, extreme weakness.

With this question in mind, we have studied a series of patients who were addicted either to morphine or to heroin. We believe that the underworld type, which constituted the greater percentage of our cases, is the best group for this study as they have been subject to the various factors mentioned by Terry and Pellens [1] which have clouded the issue of physical deterioration and physical fitness. Our studies consisted in measuring the weights, heights and vital capacities, making thorough physical examinations and subjecting the patients to Schneider's test of physical fitness during the administration of a sufficient amount of morphine to supply their needs, and comparing these observations with normal standards.

### PHYSICAL EXAMINATION

A careful examination in ninety-six cases together with information gained from the supervision of the physical examination in 450 additional cases by the interns on service gave the following results:

The large majority of the patients were between the ages of 20 and 40 and their physical status conformed closely to that of the normal persons of that age and group. Some showed emaciation which sometimes reached an extreme degree, but many were muscular and well developed and a number were obese.

1. Terry, Charles E., and Pellens, Mildred: The Opium Problem, Camden, N. J., Haddon Craftsmen, 1925.

The skin was sallow in many cases, but this change in color was practically always present in patients who lived a rather unhygienic, sedentary life. On the other hand, the skin of those who followed healthy outdoor occupations had the color of excellent health.

Distribution of hair conformed to that of normal persons. A few showed premature grayness, but the incidence was not out of proportion to that for the general population.

Fig. 1.—Scar formation; the result of six months' hypodermic administration of heroin.

Sixty per cent of these ninety-six patients showed scars of previous abscesses, and 5 per cent had active abscesses on admission to the hospital. These were usually found over the upper arms, abdomen, thighs and buttocks. Several types of scars were noted. The older marks were pale bluish discolorations just below the skin which the patients declared were due to cocaine. The more recent marks were the result of abscesses caused by improperly disinfected hypodermic needles or by the irritating diluents used with either morphine or heroin; the average diameter of the abscesses was about 4 cm. The abscesses when

healed left depressed, cicatrized scars. The subcutaneous tissue of the arms, thighs and abdomen was quite frequently the seat of a good deal of induration, and often small, isolated, nodular masses could be palpated. We have seen one case of tetanus develop from suppurating abscesses.

The pupils were practically always contracted when the patient had had his usual quantity of the drug. They reacted to light and in accommodation, though somewhat more sluggishly than normally. In three patients (3.3 per cent) who had been addicted for periods of more than ten years, the contraction of the pupils was absent during administration of the drug. The extra-ocular movements were normal.

Fig. 2.—Points of injection with discoloration over superficial veins of forearm and arm, in addict using 20 grains (1.3 Gm.) of morphine intravenously daily for a period of six months.

The eyegrounds did not show any abnormality of either the retina or the vessels.

The nose rarely (2 per cent of our cases) presented a perforated septum as a result of the patient sniffing cocaine. In 40 per cent of our cases we encountered considerable congestion of the nose and nasopharynx with increased secretion and consequent difficulty in breathing through the nostrils.

Sixty per cent of the ninety-six patients examined exhibited a particularly high degree of pyorrhea and dental caries. Before attributing these changes to the continued use of drugs, one must bear in mind that these people are notorious in their lack of care of the teeth and

failure to consult a dentist. Two per cent had suppurating abscesses about the teeth. A tremor of the tongue was present in 4 per cent of the patients examined. Otherwise, the oral cavity showed nothing abnormal. The throat (40 per cent) showed a chronic inflammatory condition, but these persons are excessive smokers, a factor to be borne in mind.

The thyroid was not palpable in a single case. The chest was, as a rule, of normal shape with good expansion. In four cases inactive fibroid tuberculosis was present, which was confirmed by roentgen examination. The heart was normal in size as determined by percussion,

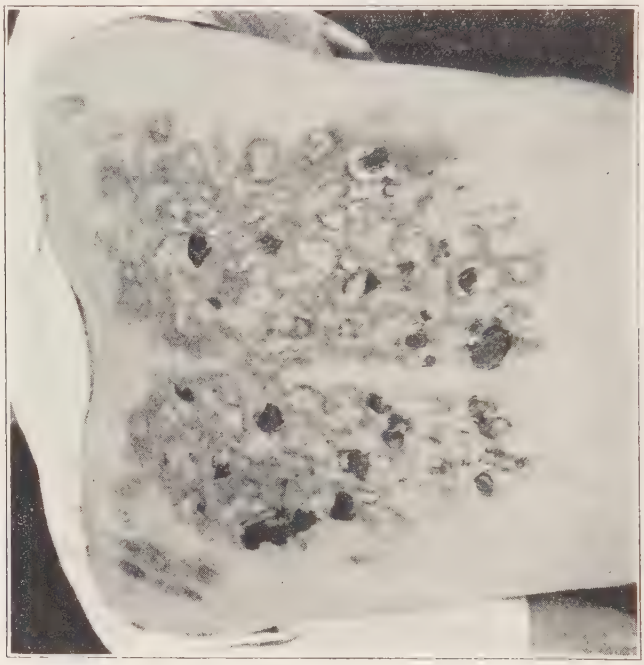

Fig. 3.—Active abscesses, the result of two months' hypodermic injections of 70 grains (4.5 Gm.) of heroin daily by a fellow addict.

and the apex beat was in the normal position. Thrills were not present on palpation in any case. Heart sounds were of good quality, and in only one case of the ninety-six was a systolic mitral murmur present, with no evidence of cardiac decompensation. The heart rate was slow in most cases, the average being 68 beats per minute. There was evidence of sclerosis of the peripheral vessels in only one patient, a man, aged 64, who had a degree of sclerosis consistent with his age. He had been using morphine for thirty-two years.

The abdomen was soft and enlargement of the liver or spleen was not noted, nor were we able to elicit any tenderness in the liver. Fecal

masses were often palpable in the descending colon. The extremities were, as a rule, poorly developed, except in patients who performed manual labor or engaged in exercise; in such persons the extremities were proportionately developed. Definite tremor of the outstretched hands was encountered in 4 per cent of our cases. The degree of staining of the fingers due to cigaret smoking is extreme.

### WEIGHTS AND VITAL CAPACITIES

*Methods.*—One hundred men were examined for age, weight and height, and comparisons were made with figures considered normal by the Mutual Life Insurance Company of New York. An allowance of 5 pounds (2.3 Kg.) was made for the weight of clothing in the insurance weight tables. Vital capacities were determined in eighteen cases and

*Weights and Vital Capacities of Opium Addicts During the Administration of Morphine*

| | Number of Cases Above Normal | Number of Cases Below Normal | Highest Value, per Cent | Lowest Value, per Cent | Average for Group, per Cent |
|---|---|---|---|---|---|
| Weight compared with normal weight for height and age.. | 43 | 53 | +35 | —24 | + 0.2 |
| Vital capacity compared with Dreyer's normal using observed weight | | | | | |
| Dreyer's class B..... | 10 | 8 | +22 | —30 | + 2.6 |
| Dreyer's class C..... | 12 | 6 | +32 | —25 | + 9.6 |
| Using subject's normal weight for height | | | | | |
| Dreyer's class B..... | 10 | 8 | +22 | —17 | + 3.4 |
| Dreyer's class C..... | 15 | 3 | +30 | —11 | +10.5 |

were compared with Dreyer's table,[2] both actual weights and normal weights for height and age being used.

*Results.*—Ten persons in the group of 100 studied, whose height and weight were measured, varied 20 per cent from the normal weight for the age and height; these ranged 35, 31, 29, 28, 26 and 21 per cent above and 25, 24, 24 and 24 per cent below. The average weight above normal in the forty-three cases above the mean normal was 18 pounds (8.2 Kg.), the average weight below normal in the fifty-three cases below the mean normal was 19 pounds (8.6 Kg.). The average of the entire group of 100 cases was only 0.2 per cent above normal. The average length of addiction of the patients showing weights above the normal figures was 10.5 years, with an average daily dosage of either heroin or morphine of 21 grains (1.36 Gm.). The average length of addiction of the persons with weights below normal was 9.5 years, with a daily consumption of 22 grains (1.4 Gm.) of drugs.

2. Dreyer, Georges, and Hanson, G. F.: The Assessment of Physical Fitness, London, Cassell & Co., 1920, pp. 115.

Vital capacities in eighteen cases were compared with Dreyer's classes, which are as follows:

Class A: Army and Navy personnel, and any person who has undergone prolonged training in either service independent of his ordinary vocation in life.
Police force.
Athletes and active sportsmen.
University students (playing games).
Fire brigade.
Blacksmiths and boilermakers.

Class B: Professional classes (doctors, lawyers, etc.).
Business men.
Railwaymen.
High grade mechanics.
Clerks, upper class.

Class C: Tailors.
Shopkeepers.
Shoemakers.
Printers.
Potters.
Clerks, lower class.
Painters.

Our subjects classified as to occupations according to their own statements, which of course are subject to question, were: four chauffeurs, two bookbinders, one salesman, one farmer, one printer, one driving instructor, one draftsman, one foreman in a garage, one miner, one cook on a ship, one railroad employe, one brass finisher, one reporter and one unknown. They belong, therefore, in Dreyer's classes B and C. No constant significant deviation from the normal was observed; the vital capacities, when they varied from the normal, tended to be high rather than low for classes B and C.

## PHYSICAL FITNESS

Schneider's test [3] was applied thirty-one times on twenty-one subjects during the administration of morphine. The resulting scores range from 1 to 17. In seventeen of these subjects the scores range from 10 to 17. The remaining four cases scored as follows: one case, 9 points; the second case, 8 and 12; the third, 1 and 5 and the fourth case, 6, 4 and 11. A perfect score indicating the ideal physical fitness is 18 points.[3] The test is based on pulse rates taken while the patient is reclining and standing, a comparison of the two, changes in blood pressure while the patient is reclining and standing and the increase in heart rate after slight exercise as well as the speed of return to normal.

3. Schneider, Edward C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

Our subjects all scored well in the various determinations necessary except for the change in pressure when they changed from the reclining to the standing posture; in practically all cases, there was a tendency to a fall rather than a rise in pressure. Schneider [4] attributed this in many cases to excessive cigaret smoking, which invariably is noted in our cases. The low score of only 1 point obtained in one of our cases was in a person who was extremely neurotic but who did not show evidence of organic disease. There is no correlation between the various scores and length of addiction, daily dosage and age. Schneider [4] considered a score below 9 points as indicative of organic disease or unhygienic living.

### COMMENT AND LITERATURE

We have been unable to find in the literature any data on actual weights, heights, vital capacities and tests of physical fitness in the opium addict. The various statements made in reference to opium addiction and its effects on physical appearance and physical fitness apparently are based on limited inspection. Levinstein,[4a] Osler [5] and Lambert [6] agreed that the drug may be used for months before any signs of emaciation appear. Osler [5] and Lambert [6] also stated that some persons can use the drug for several years without showing emaciation. Kraepelin [7] called attention to the fact "of how little the symptoms of the disease may catch the eye." Bishop [8] advanced the theory "that the same power which locked up the opiate in the body also locked up the toxic products of tissue metabolism." According to Bishop,[8] if the addict maintains "good elimination" he will escape detection and not show any signs of physical deterioration for years. In the few recognized cases of opium addiction that have come to autopsy, whether the drug was being taken at the time of death or not, the pathologic changes found have been insignificant (Ball,[9] Anders and Musser,[10] and Allbutt [11]).

4. Schneider, Edward C., and Truesdell, Dorothy: Daily Variations in Cardio-Vascular Conditions and a Physical Efficiency Rating, Am. J. Physiol. **67**:193 (Dec.) 1923.

4a. Levinstein, Edward: Die Morphiumsucht, tr. by Charles Harrer, 1878.

5. Osler, W.: The Principles and Practice of Medicine, 1894, ed. 6, New York, D. Appleton & Company, 1905, pp. 1160.

6. Lambert, A.; In Nelson's Looseleaf Medicine, New York, Thomas Nelson & Sons, 1920.

7. Kraepelin, Emil: Lectures on Clinical Psychiatry, tr. from ed. 2 (German) rev. and ed. by Thomas Johnstone, ed. 3, London, Bailliere, Tindall & Cox, 1913.

8. Bishop, Ernest S.: Narcotic Drug Problem, New York, The Macmillan Company, 1920, p. 47.

9. Ball, B.: Des lésions de la morphinomanie, et de la presence de la morphine dans les viscères, Encéphale, 1887.

10. Anders, J. M., and Musser, J. H.: Practice of Medicine, Philadelphia, W. B. Saunders Co., 1920.

11. Allbutt, Thomas C.: A System of Medicine, London, The Macmillan Company, 1905.

Bishop [8] and Morat [12] both stated that they found not only enlargement of the liver, but tenderness over this area during addiction. We have been unable to confirm this observation in any case in which morphine was being administered in sufficient quantities to prevent withdrawal symptoms. The contracted pupils are by far the most constant physical sign, as most observers state, and may justify one in considering the possibility of addiction.

We do not doubt the existence of the extreme cases of emaciation reported in the literature. It is inevitable that some users of opium will at a certain time in their lives reach this degree of physical impairment. Sooner or later, the great majority exhaust their funds, and it becomes a matter of either drugs or food. At this point they invariably purchase drugs. They tend then to resort to cures or to attempt themselves to reduce their dosage, with consequent withdrawal symptoms.

This point is best illustrated by one of our patients who immediately after his first treatment in our ward again began the use of the drug when discharged from the hospital. Within a period of two months, during which time he was unable to obtain a sufficient amount of the drug and sufficient food, he lost 30 pounds (13.6 Kg.). He then returned to our ward where the drug, in quantities sufficient to prevent withdrawal symptoms, and abundance of food were administered for several days before treatment was begun. He showed a rapid gain in weight in this short period before treatment.

There is a direct ratio between the decline in strength and weight and the number of times the addict curtails his food in order to get the drug. We agree with the statement of Bishop [8] that if the drug is used in sufficient amounts in relatively normal hygienic surroundings, the opium addict will escape detection for years and will not show any obvious physical deterioration or impaired physical fitness.

## CONCLUSIONS

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine.

We believe that the existence of considerable emaciation in certain cases is caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug.

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12. Morat, D.: Le sang et les secretions au cours de la morphinomanie et de la desintoxication, Paris, G. Steinheil, 1911, p. 180.

## III. THE CIRCULATION AND RESPIRATION OF HUMAN ADDICTS DURING THE ADMINISTRATION OF MORPHINE

The data presented in this paper have been accumulated from the study of a number of opium addicts for the purpose of determining whether prolonged addiction to the drug or its derivatives has brought about any detectable changes in the behavior of the circulatory system. We have studied the heart and circulation not only while the addict was at rest in bed but when he was subjected to a standardized physical task. As a basis for comparison, similar tests were conducted on trained and untrained persons not addicted to opium. This paper also includes an electrocardiographic study as well as orthodiagrammatic measurements of addicts while morphine was being administered. It also contains the effects of the injection of atropine sulphate on the heart rate and P-R interval in a series of addicts while they were receiving morphine.

### EXPERIMENTAL PROCEDURE

All the experiments and measurements were performed during the morning, usually between 9 and 12. The addicts were not given any breakfast when studies were to be made. In all cases, the subjects were receiving morphine at regular intervals, the amounts ranging between 6 and 28 grains (0.4 and 1.82 Gm.) per day, enough to supply their needs.

The basal pulse rates, blood pressures and respiration rates were obtained after the subjects had been reclining in bed for half an hour.

The figures for the blood pressure are the average of as many as could be accurately taken in a period of five minutes. The figures for the pulse and respiration rates are the average of a continuous five minute count. The figures obtained while the addict was standing were always made following those obtained while he was reclining. Following this period, he was asked to stand quietly in the erect posture, partially supported by the wall or window, and was not allowed to move except for a slight occasional shifting of the position of the feet. He was allowed to stand for five minutes, when again a series of determinations of blood pressure was made for a period of five minutes as well as a continuous count of the pulse rate; the figures were then averaged.

The electrocardiographic records before and after the injection of atropine were made for us by Dr. Thomas MacMillan, who is in charge of the electrocardiographic work in the Philadelphia General Hospital. The nine addicts selected for these tests were sent to this department without breakfast and rested in a chair for from fifteen to thirty

minutes before records were made. Following the taking of the record after this rest period, each addict was given $\frac{1}{20}$ grain (3 mg.) of atropine sulphate hypodermically, and records were taken every three or four minutes for the next hour and a half.

The staircase climbing test was carried out on addicts and nonaddicts; some of the latter were athletes in active training, members of the varsity crew and track teams of the University of Pennsylvania. The nonathletes were made up largely of interns from the Philadelphia General Hospital as well as of the members of the staff investigating this problem. None of the group of nonathletes was engaged in any form of systematic exercise, and all were leading a more or less sedentary life.

All subjects on whom the staircase climbing test was carried out, regardless of the group, abstained from breakfast and reclined in bed for thirty minutes before the basal blood pressure, and pulse and respiration rates were determined during a five minute period. They then walked slowly down the two flights of stairs. They were allowed to sit on the lower step for five minutes to rest preliminary to their climb. At the end of this five minute rest period, the climb was immediately begun, the subject being paced by one of the observers, each taking two steps at a time. A stop watch was used so that the length of time required to travel up the stairs was practically the same in all cases, varying from eighteen to twenty-one seconds. The task of climbing the fifty-four steps was arduous, because the time was so short that the subject was required to run at top speed, taking two steps at a time. As soon as the subject arrived at the top of the staircase, he lay down at once on the bed, and blood pressure, pulse and respiration rates were determined. Determinations of blood pressure were made continuously for five minutes, while a continuous record of the pulse and respiration rates was taken. The first determinations of blood pressure, pulse and respiration rates are recorded separately in the tables and charts. Following this, the blood pressures were averaged for each minute, and the respiration and pulse rates given per minute.

## RESULTS

In table 1 are summarized the figures for the blood pressures and pulse rates of a group of addicts, both while they were reclining and while they were standing, together with the respiration rate while they were reclining. Of the fifty patients whose pulse rate was studied while they were reclining, fifteen showed a rate between 50 and 60 a minute, twenty-four between 60 and 70, eight between 70 and 80 and three between 80 and 85. The individual pulse rates taken while the patients were standing were: 1 case, below 60, four cases between 60 and 70,

thirteen cases between 70 and 80, six cases between 80 and 90, five cases between 90 and 100 and one case at 112.

The range of systolic pressures while the forty subjects studied were reclining showed only one pressure below 100 mm., namely, 98 mm. In nine cases the pressures were between 100 and 110, in fifteen cases between 110 and 120, in twelve cases between 120 and 130 and in three cases between 130 and 140. The systolic pressures obtained in twenty-eight addicts while standing were distributed as follows: in one case, between 80 and 90; in three cases, between 90 and 100; in sixteen cases, between 100 and 110; in three cases, between 110 and 120; in four cases, between 120 and 130, and in one case between 130 and 140. The determination of the diastolic pressures of the forty reclining subjects studied resulted in two between 50 and 60, sixteen between 60 and 70, sixteen between 70 and 80, and six between 80 and 90. Diastolic pressures taken while the subject was

TABLE 1.—*Blood Pressure, Pulse and Respiration Rate of Human Addicts During the Administration of Morphine*

| | Pulse Rate | | Blood Pressure | | |
|---|---|---|---|---|---|
| | Patient Reclining | Patient Standing | Patient Reclining | Patient Standing | Respiration |
| Number of cases | 50 | 30 | 40 | 28 | 43 |
| Highest | 84 | 112 | 138/92 | 138/89 | 22 |
| Lowest | 52 | 66 | 98/62 | 88/64 | 10 |
| Average | 65 | 79 | 117/72 | 108/74 | 18 |

standing were: between 60 and 70 in five cases; between 70 and 80 in fifteen cases, and between 80 and 90 in ten cases.

Of the forty addicts in whom the respiratory rate was studied while they were reclining, the rate of six fell between 10 and 15 per minute, of thirty between 15 and 20 and of fourteen between 20 and 22 per minute.

Table 2 contains a summary of the electrocardiographic studies of nine addicts together with the effects of the administration of $\frac{1}{20}$ grain (3 mg.) of atropine sulphate. The average pulse rate of these addicts was 75.8 per minute, and the average P-R interval, 0.157 second. Both auricular and ventricular complexes were normal in all the leads in all cases. Of the nine cases studied, the P-R interval in one case was 0.18 second; in three cases 0.16 second; in one case 0.15 second; in three cases 0.14 second, and in one case 0.13 second. The average decrease of the P-R interval due to the effects of the atropine sulphate was 0.26 second, the individual results being: in one case, a decrease of 0.05 second; in two cases, 0.04 second; in two cases, 0.02 second, and in two cases, 0.01 second. The percentage increase in the rate after the administration of atropine, while averaging 45.7 per cent, was

distributed as follows: in one case it increased to 21 per cent, in three cases between 30 and 40 per cent, and in four cases between 50 and 60 per cent. The time of the greatest effect of the atropine sulphate on the P-R interval averaged fourteen and a half minutes. Of the individual cases, one showed the greatest effect in seven minutes, two cases in nine and a half minutes, two cases in twelve minutes, and the rest distributed as follows, namely, fourteen minutes, twenty-two minutes and thirty-six minutes, respectively.

TABLE 2.—*Summary of Electrocardiographic Studies in Human Addicts During the Administration of Morphine Together with the Effects of the Administration of One Twentieth Grain of Atropine Sulphate*

| | Rate Before Atropine | Rate During Height of Atropine Effect | Per Cent Increase | Time of Greatest Effect | P-R Interval Before Atropine | P-R Interval During Height of Atropine Effect | Decrease in P-R Interval | Time of Greatest Effect |
|---|---|---|---|---|---|---|---|---|
| No. of cases.... | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| Highest..... | 90 | 125 | 60 | 36 min. | 0.18 | 0.15 | 0.05 | 36 min. |
| Lowest..... | 54 | 81 | 21 | 16 min. | 0.14 | 0.11 | 0.01 | 7 min. |
| Average..... | 75.8 | 101.3 | 45.9 | 24.7 min. | 0.157 | 0.13 | 0.027 | 14.5 min. |

TABLE 3.—*A Comparison of the Cardiac Response to Staircase Climbing as Shown by Pulse Rate in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

| | Basal | First Reading | First Minute | Second Minute | Third Minute | Fourth Minute | Fifth Minute |
|---|---|---|---|---|---|---|---|
| Addicts (22 tests) | | | | | | | |
| Highest..... | 82 | 152 | 127 | 111 | 101 | 95 | 93 |
| Lowest..... | 51 | 92 | 77 | 62 | 56 | 55 | 59 |
| Average..... | 64 | 126 | 101 | 84 | 77 | 75 | 76 |
| Athletes (11 tests) | | | | | | | |
| Highest..... | 79 | 128 | 96 | 72 | 77 | 76 | 79 |
| Lowest..... | 56 | 110 | 78 | 50 | 50 | 52 | 56 |
| Average..... | 67 | 117 | 84 | 65 | 67 | 66 | 68 |
| Nonathletes (10 tests) | | | | | | | |
| Highest..... | 89 | 152 | 125 | 107 | 102 | 107 | 103 |
| Lowest..... | 61 | 104 | 82 | 62 | 60 | 62 | 74 |
| Average..... | 75 | 126 | 107 | 91 | 88 | 87 | 87 |

Figure 1 is a typical tracing obtained from an addict, a man, aged 26, who received 12 grains (0.78 Gm.) of morphine sulphate every twenty-four hours. His history of addiction extends over a period of eight years, during which time he claimed to have used as much as 25 grains (1.6 Gm.) of morphine a day.

Tables 3 to 6 inclusive contain the summaries of the response of the blood pressure, heart and respiratory rate to staircase climbing in a group of twenty-two addicts compared to these results for eleven athletes and ten nonathletes. Comparison of the average pulse rate reaction in the groups shows that the initial increase in the rate of the addicts was 12 beats more than the rate of the athletes, and 11 more

than that of the nonathletes. At the end of the five minute observation period, the addicts' average rate was still 11 beats above the basal level, that of the nonathletes 12 beats and that of the athletes only one beat above their individual basal levels.

The initial increase in systolic pressure was greatest in the athletes, namely, 45 mm.; it was 33 mm. in the nonathletes and 29 mm. in the addicts. At the end of five minutes, all three groups showed an average of 4 mm. above the basal systolic pressure. A comparison of the results of the determinations of the diastolic pressures showed an initial fall of 10 mm. in the addicts, 22 mm. in the nonaddicts and 10 mm.

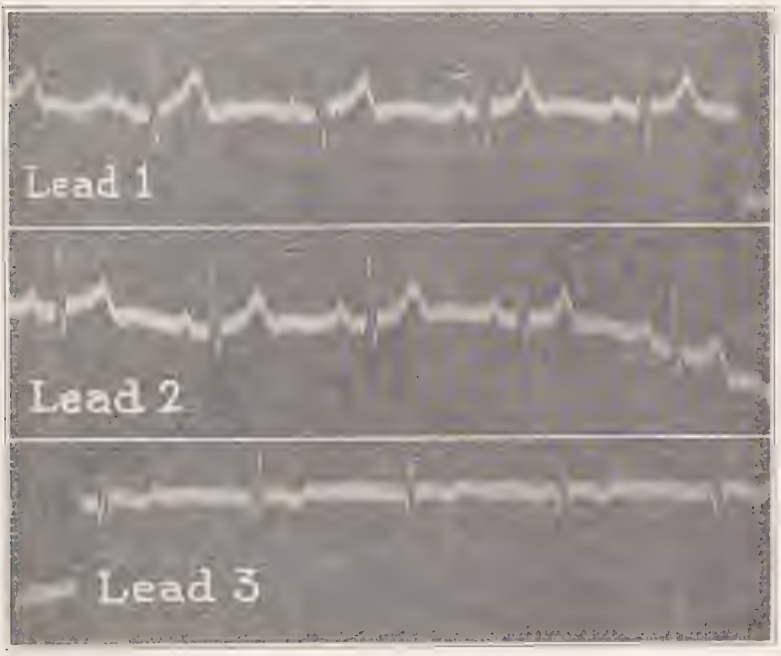


Fig. 1.—Electrocardiographic tracing obtained from a male opium addict, who has used morphine for eight years. The daily dose in the ward was 12 grains (0.78 Gm.) of morphine sulphate.

in the athletes. At the end of the five minute rest period, the diastolic pressure of the athlete was still 5 mm. below the basal pressure for the athlete, 4 mm. above for the nonathlete and 6 mm. below for the addict.

The changes in the respiratory rate showed an initial increase of 4 respirations per minute in the athlete, 7 in the nonathlete and 5 in the addict. Five minutes later, the average rate of the athletes was again normal, while those of the nonathlete and the addict were still one above.

The orthodiagrammatic measurements made of the heart of eight different addicts resulted in a range of the ratio of the transverse

TABLE 4.—*A Comparison of the Systolic Pressure Response to Staircase Climbing in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

| | Basal | First Reading | First Minute | Second Minute | Third Minute | Fourth Minute | Fifth Minute |
|---|---|---|---|---|---|---|---|
| Addicts (22 tests) | | | | | | | |
| Highest | 135 | 176 | 180 | 164 | 151 | 138 | 131 |
| Lowest | 97 | 106 | 110 | 106 | 106 | 102 | 98 |
| Average | 116 | 145 | 146 | 141 | 132 | 125 | 120 |
| Athletes (11 tests) | | | | | | | |
| Highest | 138 | 178 | 180 | 165 | 148 | 139 | 132 |
| Lowest | 100 | 138 | 140 | 124 | 116 | 111 | 111 |
| Average | 119 | 164 | 160 | 145 | 132 | 126 | 123 |
| Nonathletes (10 tests) | | | | | | | |
| Highest | 135 | 168 | 178 | 160 | 151 | 139 | 138 |
| Lowest | 108 | 126 | 130 | 125 | 122 | 119 | 115 |
| Average | 116 | 149 | 150 | 141 | 134 | 128 | 124 |

TABLE 5.—*A Comparison of the Diastolic Pressure Response to Staircase Climbing of Human Addicts During the Administration of Morphine and of Athletes and Nonathletes*

| | Basal | First Reading | First Minute | Second Minute | Third Minute | Fourth Minute | Fifth Minute |
|---|---|---|---|---|---|---|---|
| Addicts (22 tests) | | | | | | | |
| Highest | 82 | 80 | 80 | 80 | 79 | 83 | 81 |
| Lowest | 52 | 38 | 52 | 44 | 51 | 53 | 52 |
| Average | 70 | 60 | 63 | 64 | 64 | 64 | 64 |
| Athletes (11 tests) | | | | | | | |
| Highest | 77 | 80 | 70 | 82 | 78 | 78 | 75 |
| Lowest | 54 | 28 | 40 | 42 | 30 | 30 | 40 |
| Average | 66 | 55 | 60 | 62 | 60 | 59 | 61 |
| Nonathletes (9 tests) | | | | | | | |
| Highest | 91 | 74 | 78 | 73 | 75 | 79 | 77 |
| Lowest | 60 | 20 | 60 | 58 | 55 | 53 | 54 |
| Average | 70 | 52 | 74 | 63 | 74 | 72 | 74 |

TABLE 6.—*A Comparison of the Response of Respiration to Staircase Climbing in Human Addicts During the Administration of Morphine and in Athletes and Nonathletes*

| | Basal | First Minute | Second Minute | Third Minute | Fourth Minute | Fifth Minute |
|---|---|---|---|---|---|---|
| Addicts (22 tests) | | | | | | |
| Highest | 19 | 28 | 24 | 22 | 20 | 21 |
| Lowest | 12 | 17 | 14 | 11 | 11 | 13 |
| Average | 16 | 21 | 18 | 17 | 17 | 17 |
| Athletes (11 tests) | | | | | | |
| Highest | 22 | 27 | 27 | 27 | 25 | 25 |
| Lowest | 10 | 14 | 11 | 11 | 10 | 10 |
| Average | 14 | 18 | 15 | 15 | 14 | 14 |
| Nonathletes (9 tests) | | | | | | |
| Highest | 22 | 30 | 27 | 26 | 22 | 22 |
| Lowest | 11 | 19 | 16 | 15 | 13 | 13 |
| Average | 16 | 23 | 21 | 19 | 18 | 17 |

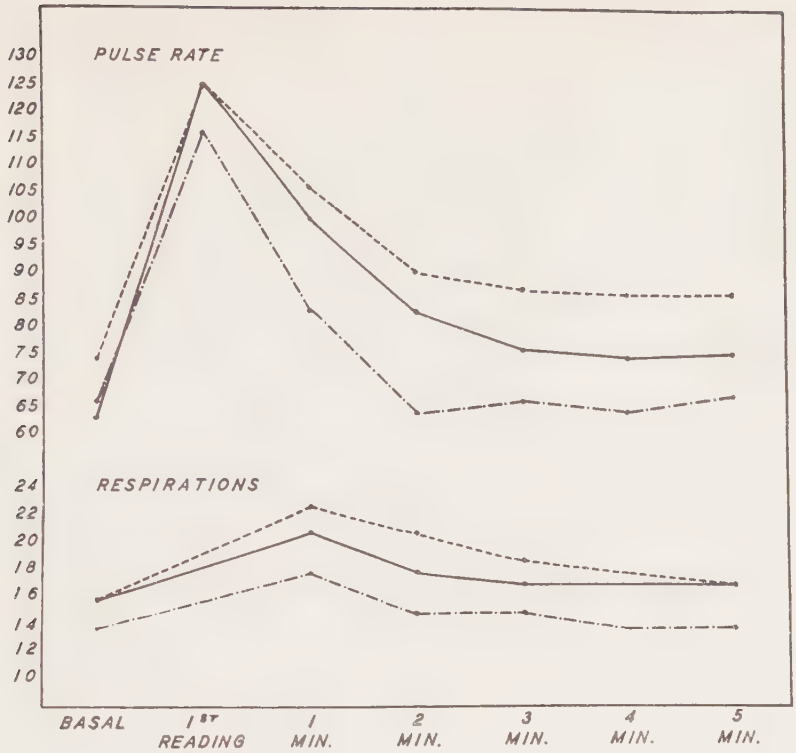


Fig. 2.—Average changes in pulse and respiration rates in a group of human addicts receiving morphine, nonaddicts and athletes, following the staircase climbing test. In this and fig. 3, the solid line indicates addicts; the broken line, nonaddicts, and the dash and dot line, athletes.

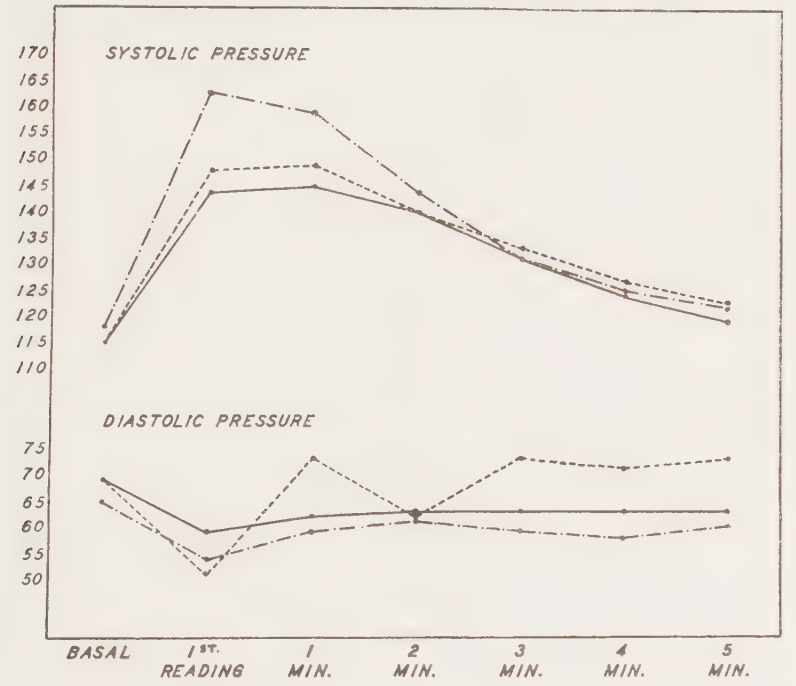


Fig. 3.—Average changes in systolic and diastolic blood pressure in a group of human addicts receiving morphine, nonaddicts and athletes, following the staircase climbing test.

diameters of the heart to the chest of from 38.2 to 50 per cent. Of the eight cases in table 7, the ratios in four were within the normal range of Danzer,[1] namely, from 45 to 50 per cent. In three the ratio fell between 45 and 40 per cent and in one it was 38.2 per cent. All cases showed a diameter of the aortic arch of less than 6 cm., ranging from 4.1 to 5.6 cm., with an average of 4.8 cm.

## COMMENT AND LITERATURE

A careful study of the data presented in this paper does not reveal any obvious deviation from the normal of the heart and circulation in human opium addicts during the administration of morphine sulphate to prevent withdrawal symptoms. The literature covering this subject in human addicts is limited to general statements regarding the circulation.

TABLE 7.—*Measurements of the Heart Obtained from Orthodiagram of Addicts During the Administration of Morphine*

| Case Number | Aortic Arch, Cm. | Transverse Diameters of Heart, Cm. | Transverse Diameters of Chest, Cm. | Ratio of Transverse Diameters, per Cent |
|---|---|---|---|---|
| 26-32 | 4.1 | 11.5 | 28.3 | 40.6 |
| 26-34 | 5.0 | 12.9 | 26.0 | 49.6 |
| 26-21 | 5.6 | 12.3 | 27.8 | 47.8 |
| 26-35 | 5.4 | 12.6 | 26.8 | 43.2 |
| 26-31 | 4.1 | 10.8 | 28.2 | 38.2 |
| 26-30 | 5.2 | 12.3 | 28.1 | 43.7 |
| 26-39 | 4.5 | 15.3 | 31.0 | 49.3 |
| 26-29 | 4.8 | 13.1 | 26.2 | 50.0 |
| Average | 4.8 | 12.5 | 27.8 | 45.3 |

Levinstein,[2] one of the earliest writers on opium addiction in man, asserted that addicts frequently suffered with dyspnea and palpitation of the heart. He described the pulse as often being small and rather hard. Jouet [3] mentioned frequency of palpitation and precordial pain. Bell [4] and Schwenninger [5] claimed the presence of fatty degeneration of the heart, but Allbutt [6] did not believe this, because of evidence obtained at clinical examination or at autopsy. At an autopsy performed on an

1. Danzer, C. Saul: The Cardiothoracic Ratio: An Index of Cardiac Enlargement, Am. J. M. Sc. **157**:513 (April) 1919.

2. Levinstein, Edward: Die Morphiumsucht, trans. by Charles Harrer, 1878.

3. Jouet, D.: Étude sur le morphinisme chronique, Thèse de Paris, 1883.

4. Bell, F. M.: Morphinism and Morphinomania, New York M. J. **93**:680, 1911.

5. Schwenninger, Ernst: Gesammelte Arbeiten, Berlin, 1886, vol. 1, chapter 4, pp. 143-151.

6. Allbutt, T. C.: A System of Medicine. London. The Macmillan Company, 1908, vol. 2, part 1.

opium addict thirteen days after withdrawal of the drug, Ball [7] found slight myocardial degeneration but not sufficient to cause death. Pettey [8] believed in the presence of defective heart action, while Church and Peterson [9] included cardiac weakness, intermittence and bradycardia among the symptoms of opium addiction. Lambert [10] called attention to the slow pulse of the morphinist and stated that in the later stages there was a fall in arterial tension and enfeeblement of the heart. De Fursac and Rosanoff [11] claimed not only the occurrence of circulatory atony and weak cardiac impulse, but also of transient edemas in addicts. Sollman [12] and Anders and Musser [13] mentioned the frequent presence of cardialgia. Bishop [14] also called attention to the slow pulse of the morphinist. Sandoz [15] reported that addicts often complained of palpitation of the heart with rapid and irregular pulse accompanied with fainting spells. Legewie [16] studied the behavior in a case of morphine addiction from its inception to death. Despite attacks of delirium and motor excitations which could be relieved by additional amounts of morphine, at no time did the patient show any weakness of the circulatory system.

In a series of 96 patients in whom the behavior of the circulation was studied, not one complained of attacks of cardialgia. The history of the presence of palpitation was sometimes elicited when the addict was certain that he was not using sufficient quantities of the drug to prevent withdrawal symptoms. Two of the 96 cases showed occasional extrasystoles; otherwise, irregularity of the pulse was never encountered. Normal figures for the basal pulse rate, blood pressure and respirations vary, as shown in the literature. All the figures that we

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7. Ball, B.: Des lésions de la morphinomanie, et de la présence de la morphine dans les viscères, Encéphale, 1887.

8. Pettey, G. E.: Narcotic Drug Diseases and Allied Ailments, Philadelphia, F. A. Davis and Co., 1913.

9. Church, A., and Peterson, F.: Nervous and Mental Diseases, ed. 8, Philadelphia, W. B. Saunders Company, 1914, pp. 930.

10. Lambert, A., in Osler and McCrae: Modern Medicine, Philadelphia, Lea & Febiger, 1914, vol. 2, chapter 23, pp. 396.

11. De Fursac, Rogues J., and Rosanoff, A. J.: Manual of Psychiatry, New York, John Wiley & Sons, 1916.

12. Sollman, Torald: Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1917, pp. 355.

13. Anders, J. M., and Musser, J. H.: Practice of Medicine, Philadelphia, W. B. Saunders Company, 1920.

14. Bishop, E. S.: Morphinism and Its Treatment, J. A. M. A. **58**:1499 (May 18) 1912.

15. Sandoz, C. E.: Report on Morphinism to the Municipal Court of Boston, J. Crim. Law & Criminol. **13**:1 (May) 1922.

16. Legewie, B.: Delirium bei Morphinismus: Zugleich ein Beitrag zur Frage der Morphingewohnung, Ztschr. f. d. ges. Neurol. u. Psychiat. **89**:558, 1924.

obtained, however, lie well within the normal variations. The average systolic blood pressure in a large series of normal subjects reported by Fisher [17] was 123.2 mm., while in 2,000 normal patients Schneider [18] found the systolic pressure, determined while the patient was reclining, to be 117.9 mm. Our average figure for the 40 addicts while reclining was 117 mm., identical with that of Schneider and 6 mm. below the average in Fischer's cases, which may have included standing and sitting postures. Schneider's average for the pressure of the 2,000 normal men while standing was 120.2 mm.; the average in our cases was 108 mm. Schneider attributed the fall in the systolic pressures when the subjects changed from reclining to standing postures to disease, unhygienic living or excessive cigaret smoking. An analysis of our cases revealed that 75 per cent showed a fall in the pressure when the patients changed from the reclining to the standing postures. All of these subjects were excessive smokers and lived rather unhygienic lives; however, this is true of practically all our addicts.

A comparison of Schneider's normal figures for the pulse rate while the patient is reclining, which he gives as 74.1, with those in our cases, which average 65 per minute, shows a slower rate for the addicts. Guy,[19] however, in studying 100 normal subjects in the London Hospital gives an average figure of 66.6 beats per minute while the patient was reclining. Seventy per cent of the addicts we studied had a basal pulse rate below 70 per minute while reclining; this slightly slower than normal rate of the heart is in agreement with the figures of Lambert [10] and Bishop [14] for the pulse rate of morphine addicts and is suggestive of van Egmond's [20] theory that sensitiveness of the vagus center to morphine is not lost. Schneider's average normal for the pulse rate while the patient is standing is 91.9. beats per minute; Guy's average normal is 78.9 beats per minute, while our average figure is 79 beats per minute. Our figures are therefore identical with those of Guy, but considerably lower than those of Schneider.

The average respiration rate of 18 per minute in the forty cases shows the striking absence of the pharmacologic action of morphine on respiration in addicts. There was no correlation between the

17. Fisher, J. W., quoted by Norris, G. W., and Bazett, H. C.: Blood Pressure, Philadelphia, Lea and Febiger, 1927, p. 127.

18. Schneider, Edward C., and Truesdell, Dorothy: Am. J. Physiol. **61**:429 (Aug.) 1922.

19. Guy: Guy's Hosp. Rep. **4**:63, 1839; Encyclopaedia of Anatomy and Physiology, 1852, vol. 4, p. 186.

20. Van Egmond, A. A. J.: Ueber die Wirkung des Morphins auf das Herz (zugleich ein Beitrag zur Frage der Morphingewohnung), Arch. f. exper. path. u. Pharmakol. **65**:197, 1911.

amounts of the drug administered to these addicts and the individual variations in respirations.

The electrocardiographic tracings were analyzed and did not show fundamental differences from those obtained in a series of normal subjects in this hospital or from those published by Lewis.[21] In a study of the determination of the average P-R interval in normal patients, Lewis and Gilder stated that it is usually between 0.13 and 0.16 seconds. Our average figure for nine cases is 0.157 second, this figure being placed near their upper limits. Three of the nine cases showed P-R intervals above the average of 0.157 second; in one case, the interval was 0.18 second and in two, 0.16 second. We have no data at hand for comparison of the action of atropine in normal persons, but these results are given here as the same experiments were performed, and will be reported in a later paper, on the same subjects after the drug had been withheld for a period of six days.

Athletes were selected as one group for the study of the heart and circulation during the staircase climbing test with the object of obtaining a response which could be taken as representative of physical fitness for cardiac stress. Having obtained the reactions of the athletes, we had a basis for comparison with the addicts and untrained subjects. The response of the athletes was characterized by the greatest initial increase in systolic pressure, the least initial increase in pulse and respiration rate and the most rapid return to the normal figures. The response of the addicts compared favorably with that of the untrained nonaddicts in all respects except in the initial rise in pulse rate and blood pressure. The addicts met the strain of climbing the staircase with an increase in heart rate rather than with a rise in pressure. The readjustment to basal levels is carried out in the addict with as great rapidity as in the untrained nonaddict. The degree of perceptible dyspnea was far greater in the untrained normal subject than in the addict, who compared favorably with the athlete.

The data obtained from the orthodiagrammatic measurements of the chest suggest, that the heart of the addict is slightly smaller than the average, as in four of our cases the ratio fell below the lowest limit of the normal ratios of Danzer,[1] namely, 45 per cent. Case 26-31, in which the ratio was 38.2 per cent, did not show the slightest evidence of tuberculosis, as is suggested in cases in which the ratio falls below 45 per cent. Neither did the other three cases present any evidence of tuberculosis. The average diameter of the aortic arch does not suggest any widening in these cases.

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21. Lewis, Thomas: The Mechanical and Graphic Registration of the Heart Beat, London, Shaw & Sons, 1920.

## CONCLUSIONS

A study of the pulse rate and blood pressure while the subject is reclining and while he is standing, of the respiration, electrocardiograms and response to staircase climbing tests in a series of opium addicts, who were given morphine in sufficient quantities to prevent withdrawal symptoms, resulted in the failure to find marked deviation in the behavior of the circulation and respiration from that of normal persons.

The average pulse rate in 70 per cent of our patients while reclining was slightly below the usual average figures given for normal persons.

Orthodiagrammatic measurements showed a tendency for the heart of the addict to be smaller than the average heart in normal subjects.

## IV. THE BLOOD OF THE HUMAN ADDICT DURING THE ADMINISTRATION OF MORPHINE

In this paper, we present the data obtained from the study of blood drawn from a series of human addicts receiving morphine sulphate hypodermically in sufficient quantity to prevent withdrawal symptoms. All of these addicts exhibited the so-called withdrawal symptoms on cessation of administration of the drug. These symptoms have been described in a previous paper by us [1] and are well known to any one familiar with the drug problem. Our purpose in this study has been twofold. The first objective was to search for possible changes in the physicochemical properties of the blood of these addicts; our second, to obtain values in addicts receiving the drug for comparison with the results obtained from the same addicts following the withdrawal of the drug.

### EXPERIMENTAL PROCEDURE

During this study the addict received the quantity of drug required, which was administered to him by the nurse in charge of the ward. As a rule, the same quantity sufficed from day to day for each subject, but any minor disturbance in the ward on the part of other refractory patients always resulted in a need for a greater amount. This variation of dosage is common among addicts at liberty with a supply of the drug at hand. The slightest degree of fear on their part always resulted in a temporary increase in dosage. The dosage of the drug in the cases studied varied from 6 to 30 grains (0.4 to 1.95 Gm.) of morphine sulphate a day. The average dosage was about 20 grains (1.3 Gm.) a day.

All samples of blood were collected in the morning before breakfast while the subjects were at rest in bed. The blood was always drawn from one half to one hour after the last dose of morphine had been given. The method of collection followed was that of the investigators whose method was employed for the determination of the particular substance to be studied. Venous samples were drawn from a vein at the elbow, usually without the aid of a tourniquet; occasionally, the size of the vessels and failure to obtain enough blood without the use of the tourniquet made us resort to its aid. All estimations were begun and carried to completion immediately after the samples were obtained. The patients selected were men and were free from any abscesses or intercurrent infections.

### METHODS

To determine the hemoglobin the blood was converted to acid hematin and read colorimetrically with the Newcomer plate. The first ten readings were checked with the polariscope.[2]

1. I: The Conduct of the Addict in Relation to Investigative Study, p. 7.

2. Newcomer, H. S.: A New Optical Instrument for the Determination of Hemoglobin, J. Biol. Chem. **55**:569, 1923.

The red and white blood cell counts were made by the same person. In each case, two pipets were counted. The count was repeated if variations of 10 per cent or over were observed in counts within the normal range, or in variations of 5 per cent outside the normal range.

Differential counts were all made by the same person. From 200 to 400 cells were counted in each determination.

The volume of the red blood cells was determined by the hematocrit method, oxalated blood being used. In our experience, this method gives lower values than the centrifuge method.

In the Wassermann reaction of the blood, cholesterol and Noguchi antigens were used.

The specific gravity was measured with a 1 cc. pyknometer at 20 C.

The plasma protein was determined by a modification of the method of Howe.[3] The dry matter was determined by desiccation of 1 cc. at 105 C. to constant weight. The dry matter of the cells was calculated and is subject to appreciable error. The hydrogen ion concentration was determined by the method of Hawkins.[4] The carbon dioxide capacity of the plasma was calculated according to the method of Van Slyke and Cullen.[5]

The serum conductivity was measured with the Christiansen ionometer, expressed in milligrams of sodium chloride and corrected by the formula of Gram and Cullen.

Determinations were made of the sugar,[6] urea nitrogen,[7] creatinine,[8] uric acid,[9] cholesterol,[10] sodium chloride,[11] lactic acid[12] and serum calcium.[13]

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3. Hawk and Bergeim: Practical Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, 1926, p. 398.

4. Hawkins, J. A.: A Micro-Method for the Determination of the Hydrogen Ion Concentration of Whole Blood, J. Biol. Chem. **57**:493, 1923.

5. Van Slyke, Donald D., and Cullen, Glenn E.: The Bicarbonate Concentration of the Blood Plasma: Its Significance and Its Determination as a Measure of Acidosis, J. Biol. Chem. **30**: 289, 1917.

6. Folin, Otto; and Wu, Hsien: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367, 1920.

7. Karr, W. G.: A Method for the Determination of Blood Urea Nitrogen, J. Lab. & Clin. Med. **9**:329, 1924.

8. Folin, Otto; and Wu, Hsien: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

9. Benedict, Stanley R.: The Determination of Uric Acid in Blood, J. Biol. Chem. **51**:187, 1922.

10. Myers, Victor, C., and Wardell, Emma L.: The Colorimetric Estimation of Cholesterol in Blood with a Note on the Estimation of Coprosterol in Feces, J. Biol. Chem. **36**:147, 1918.

11. Whitehorn, J. C.: Simplified Method for the Determination of Chlorides in Blood or Plasma, J. Biol. Chem. **45**:449, 1921.

12. Friedmann, Theodore E.; Contonio, Margherita; and Shaffer, Philip A.: The Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927.

13. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

The serum magnesium was determined by precipitation of the magnesium as the ammonium magnesium phosphate and the determination of phosphate as given in the next paragraph.

The serum phosphate was expressed as milligrams of phosphorus per hundred cubic centimeters and was determined by the Benedict and Theis modification of the Briggs method.[14] The oxygen content was determined according to the procedure of Van Slyke and Stadie.[15] The sedimentation test used was that of Cooper.[16]

## RESULTS

Tables 1, 2 and 3 contain our observations in a form designed to condense them as much as possible. The tables give the normal variations for the substances investigated, the number of cases studied, the maximum, minimum and average figures, and the number deviating beyond the normal range. The number of patients studied varied greatly. Studies of the blood were continued only until we felt that we had a sufficient number of cases to establish the average and variations in addicts while they were receiving morphine.

A series of sedimentation tests done on twelve addicts are not shown in the tables. The results coincided closely with the average normal curves of Cooper.[16] Five different patients were selected for a study of the fragility of the red cells. Beginning hemolysis, from 0.44 to 0.48, and a complete hemolysis, from 0.32 to 0.36, were observed in all cases. These figures fall within normal limits. Clotting time was determined by noting the beginning of coagulation in a capillary tube. The time was noted when a soft clot was seen after the tube was broken. The average coagulation time in six cases was found to be two minutes and thirty seconds. The viscosity of whole blood was measured in five different cases by means of the Hess viscosimeter. The average viscosity of the blood was 5.18 compared to that of distilled water at a temperature of 25.4 C., the normal range being from 4.3 to 5.2. In three cases blood was drawn from the right radial artery, and the percentage saturation of the hemoglobin with oxygen was determined. The average percentage saturation in these three cases was 94.6, well within normal figures.

## COMMENT AND LITERATURE

The results obtained show data for a large number of the determinations that are well within the normal range. Certain constituents

14. Benedict, Stanley R., and Theis, Ruth C.: A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum, J. Biol. Chem. **61**:63, 1924.

15. Van Slyke, Donald D., and Stadie, William: The Determination of the Gases of the Blood, J. Biol. Chem. **49**:1, 1921.

16. Cooper, H. N.: Sedimentation Rate of Red Blood Cells, J. Lab. & Clin. Med. **11**: 615, 1926.

TABLE 1.—*The Cellular Elements of the Blood of Addicts During the Administration of Morphine*

| | Hemoglobin, Gm. per 100 Cc. | Red Blood Cells, Number per C.Mm. | White Blood Cells, Number per C.Mm. | Differential Count, per Cent | | | | | Red Blood Cells, per Cent by Volume | Blood Wassermann Reaction |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Polymorphonuclears | Lymphocytes | Large Mononuclears | Eosinophils | Basophils | | |
| Normal variation | 14.5–17 | 4,500,000–5,200,000* | 6,000–9,600* | 58–70* | 25–35* | 1–6* | 0–2* | 0–2* | 38–45 | |
| Maximum | 19.4 | 4,960,000 | 15,400 | 78 | 63 | 7 | 3 | 2 | 38.7 | Positive 3 |
| Minimum | 12.0 | 3,640,000 | 2,500 | 33 | 20 | 0 | 0 | 0 | 34.0 | Negative 28 |
| Average | 15.2 | 4,533,000 | 9,300 | 61 | 34 | 3 | ½ | ½ | 36.2 | |
| No. of cases | (26) | (29) | (33) | (28) | (28) | (28) | (28) | (28) | (6) | |
| No. of cases below normal range | 9 | 23 | 1 | 5 | 6 | 6 | 0 | 0 | 5 | |
| No. of cases above normal range | 3 | 0 | 15 | 0 | 2 | 2 | 0 | 0 | 0 | |

* Normal figures arrived at by one of us in making counts on normal persons.

TABLE 2.—*The Physical Properties, $p_H$ and Carbon Dioxide Capacity of the Blood of Addicts During the Administration of Morphine*

| | Specific Gravity | | Plasma Protein, per Cent | Dry Matter | | | Conductivity of Serum | $p_H$ of Plasma | Carbon Dioxide Capacity of Plasma, per Cent by Volume |
|---|---|---|---|---|---|---|---|---|---|
| | Blood | Plasma | | Blood, per Cent | Plasma, per Cent | Cells, per Cent | | | |
| Normal variation | 1.045–1.075 | 1.0237–1.0276 | 6.5–8.2 | 19–23 | 8–10 | 33–36 | 130–139 | 7.30–7.50 | 55–75 |
| Maximum | 1.0614 | 1.0282 | 8.3 | 22.7 | 10.2 | 48.0 | 143 | 7.51 | 71 |
| Minimum | 1.0557 | 1.0238 | 6.9 | 15.7 | 5.3 | 38.2 | 132 | 7.28 | 45 |
| Average | 1.0586 | 1.0260 | 7.8 | 20.1 | 8.4 | 41.2 | 137 | 7.36 | 57.7 |
| Number of cases | (5) | (7) | (8) | (22) | (15) | (7) | (7) | (20) | (20) |
| Number of cases below normal range | 0 | 0 | 0 | 1 | 4 | 0 | 0 | 1 | 5 |
| Number of cases above normal range | 0 | 1 | 2 | 0 | 1 | 7 | 1 | 1 | 0 |

TABLE 3.—*The Chemical Properties of the Blood of Addicts During the Administration of Morphine*

| | Blood Sugar, Mg. per 100 Cc. | Blood Urea Nitrogen, Mg. per 100 Cc. | Blood Creatinine, Mg. per 100 Cc. | Blood Uric Acid, Mg. per 100 Cc. | Blood Cholesterol, Mg. per 100 Cc. | Blood Sodium Chloride, Mg. per 100 Cc. | Blood Lactic Acid, Mg. per 100 Cc. | Serum Calcium, Mg. per 100 Cc. | Serum Magnesium, Mg. per 100 Cc. | Serum Phosphate, Mg. Phosphorus per 100 Cc. |
|---|---|---|---|---|---|---|---|---|---|---|
| Normal variation | 70–120 | 10–15 | 1–2 | 2.3–5 | 150–190 | 450–530 | 5–20 | 9–11 | 2–3 | 3–4 |
| Maximum | 122 | 24.0 | 1.3 | 4.5 | 280 | 570 | 31.13 | 14.4 | 2.12 | 3.2 |
| Minimum | 72 | 10.0 | 1.085 | 2.4 | 158 | 444 | 20.10 | 9.8 | 2.06 | 2.6 |
| Average | 97 | 13.2 | 1.160 | 3.3 | 208 | 495 | 25.75 | 10.9 | 2.09 | 2.8 |
| Number of cases | (32) | (28) | (3) | (22) | (21) | (13) | (6) | (14) | (2) | (11) |
| Number below normal range | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 7 |
| Number above normal range | 1 | 3 | 0 | 0 | 15 | 2 | 6 | 4 | 0 | 0 |

show a rather marked deviation and will be mentioned in the following discussion. We have not found any correlation between length of addiction, daily dosage, age and these deviations.

*Cellular Elements.*—We were unable to find any evidence that opium addiction per se brings about any decided decrease in the number of red cells of the blood. Our observations are in accord with those of Morat [17] and of Lambert and Tilney.[18] Morat counted the red cells in twenty-nine cases and found an average count of 5,037,000, an average white cell count of 9,300 compared to our average of 4,533,000 red cells and 9,300 white cells per cubic millimeter of blood. Lambert and Tilney [18] reported a variation of red cell counts between 4,300,000 and 4,890,000 per cubic millimeter in addicted subjects before instituting the narcosan treatment. Fuller [19] reported a single red cell count made on the blood of a heroin addict and found the number of red cells to be about 2,000,000. Gunard and Devay [20] reported a red cell count of 2,300,000 per cubic millimeter in a dog addicted to morphine for a period of six and one half months. Plant and Pierce [21] studied the blood cells of dogs which without question were really addicted for periods ranging from one to two years. They did not find variations from those of normal dogs. Our low figures were obtained from persons who lived in poor hygienic surroundings and who unquestionably suffered from lack of nourishing food due to the fact that practically all of their funds were used for drugs. The great variation in the white cell counts is difficult to explain. Morat [17] also found the same rather large variation of white cells—from 8,000 to 14,000. Our patients were free from abscesses and had normal temperatures and pulse rates. We have seen a variation of from 8,000 to 14,000 white cells per cubic millimeter in a period of three days in a patient receiving a sufficient amount of the drug.

*Chemical Elements.*—Our results are in accord with those of Lambert and Tilney [18] and of Johnson [22] for human addicts and those

17. Morat, D.: Le sang et les sécrétions au cours de la morphino-manie et la desintoxication, Paris, G. Steinheil, 1911, pp. 180.

18. Lambert, Alexander; and Tilney, Frederick: Treatment of Narcotic Addiction by Narcosan, M. J. & Rec. **124**: 764 (Dec. 15) 1926.

19. Fuller, S. C.: A Phenomenon Observed in the Blood of Morphinomaniacs, New England M. Gaz. **34**:241, 1899.

20. Gunard and Devay, F.: Observation d'un cas de morphinism chronique chez un chien, J. de med. vet. et de zootech. **19**:261, 1894.

21. Plant, O. H., and Pierce, I. H.: Studies of Chronic Morphine Poisoning in Dogs: II Changes in Blood Cells and Hemoglobin During Addiction and Withdrawal: III. Blood Sugar During Tolerance and Withdrawal, J. Pharm. & Exper. Therap. **33**:359 (July) 1928.

22. Johnson, George S.: The Use of Narcosan in the Treatment of Drug Addiction, Colorado Med. **24**:347 (Nov.) 1927.

of Plant and Pierce [21] for addicted dogs. The variations of hemoglobin reported by Lambert and Tilney [18] expressed in percentage varied between 70 and 80 were made, we understand, in addicts receiving the drug. Fuller,[19] however, in a single determination of the hemoglobin by means of the Fleischl method, reported the presence of only 20 per cent in the heroin addict he studied. Johnson [22] found only one abnormal blood sugar value in a series of twenty-four cases. Plant and Pierce [21] did not find any change in the blood sugar in their addicted dogs. The total blood cholesterol content shows a tendency to be above normal in the majority of our cases. Lactic acid is above the average normal. A number of the results of determinations of plasma inorganic phosphate are below the accepted normal of 3 mg. per hundred cubic centimenters of serum.

*Physical Properties.*—Our observations here, too, fall within the range of normal variations. Sollier [23] reported an increase in the viscosity of the blood when the number of red cells was increased in human addiction. We do not find any increase in the viscosity of the blood nor do we find any increase in the red cells. Stern-Piper [24] found the rate of sedimentation increased in nine and decreased in one of ten addicts receiving the drug. Our figures do not reveal any abnormality in this phenomenon. Morat [17] reported a diminished resistance of the red cells but gave as his normal value for complete hemolysis 0.30 and for beginning hemolysis 0.38. Our figures coincide with the figures taken as normal for these solutions in healthy subjects in this hospital.

## CONCLUSIONS

A series of addicts receiving morphine sulphate hypodermically have been studied with respect to the following determinations: hemoglobin, red blood cell count, white blood cell count, differential count, sedimentation rate, blood viscosity, cell volume, Wassermann reaction, specific gravity of the blood and plasma, plasma refractive index, dry matter of the blood and plasma, plasma $p_H$, carbon dioxide capacity of the plasma, serum conductivity, sugar, urea, creatinine, uric acid, cholesterol, chloride and lactic acid of the blood and calcium, magnesium and phosphate of the serum.

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23. Sollier, P.: Recherches sur la viscosité sanguine dans l'intoxication morphinique, Bull. Acad. de méd., Paris **87**:428 (April 18) 1922.

24. Stern-Piper, L.: Die Senkungsgeschwindigkeit des Blutes bei chronischem Morphinismus und Eukodalismus, Klin. Wchnschr. **4**:548 (March 19) 1925.

In a general way there is a tendency toward a low red cell count and a high leukocyte count, but this is not uniform in all cases. The cholesterol content was usually increased and the phosphate diminished. The lactic acid content was uniformly high. No other constituents showed any suggestive departure from the normal.

A slight degree of anemia may be present when the addict is forced to live in poor hygienic surroundings when all his funds are required to purchase the drug at the expense of sufficient nourishing foods.

# V. MISCELLANEOUS OBSERVATIONS ON HUMAN ADDICTS DURING THE ADMINISTRATION OF MORPHINE

In this paper we wish to present further results obtained from a study of a series of male opium addicts made while we were supplying their needs with morphine. These studies include fractional gastric analysis, roentgen examination of the gastro-intestinal tract, functional tests of the liver, dextrose tolerance tests, chemical and microscopic examinations of the urine, phenolsulphonphthalein tests and studies of the basal metabolic rate, temperature, blood sugar response to morphine and to epinephrine and the results of roentgen examination for persistent thymus.

## FRACTIONAL GASTRIC ANALYSIS

The secretory response of free and total acid of the stomach to the standard Ewald test meal was studied by the fractional method in eighteen different addicts. In all cases, samples of gastric juice during fasting were removed for analysis. Table 1 gives the results obtained in these cases for the contents both during fasting and at intervals of fifteen minutes following completion of the meal. As seen from the tables, both the free and the combined acid of the gastric juice during fasting varied considerably. An analysis of the individual cases showed that in six no free hydrochloric acid was present during the fasting stage. Four of these six cases still failed to show the presence of free hydrochloric acid fifteen minutes after the test meal was given. In one case, no free acid was found during the entire period of 105 minutes following the meal, while in two others in this group only small quantities were found. The other twelve cases presented a normal response of the free hydrochloric acid when compared to the observations of Rehfuss.[1]

All cases showed the presence of a certain amount of total acid in the gastric juice during fasting. The curves in chart 1 show the average of the total acid and free hydrochloric acid compared to the normal isotrophic curve of Rehfuss.[1]

A comparison of these curves shows that the curves representing the total acid of the addicts are much higher while the patient is fasting than are the normal curves, while the free hydrochloric acid is always at practically the normal level. The response of the secretion of both the free and the total acids is much slower in the addict and does not reach

1. Rehfuss, Martin E.; Bergheim, O., and Hawk, P. B.: The Fractional Study of Gastric Digestion with a Description of Normal and Pathologic Curves, J. A. M. A. **63**:909 (Sept. 12) 1914.

the magnitude of the normal curve. Both, however, reach their peaks at the same time as do the normal curves and decline at the same rate. There was no correlation between the variations in the different individual responses and the amount of drug administered or the history of length of addiction.

### ROENTGENOGRAMS OF THE GASTRO-INTESTINAL TRACT

Through the courtesy of Dr. E. Burville-Holmes, in charge of the x-ray work in the Philadelphia General Hospital, we had sixteen patients examined after the usual barium meal in order to gather what informa-

TABLE 1.—*The Fractional Gastric Analysis in Eighteen Cases of Opium Addiction During the Administration of Morphine*

| Case No. | Fasting | | 15 Min. | | 30 Min. | | 45 min. | | 60 Min. | | 75 Min. | | 90 Min. | | 105 Min. | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total | Free | Total |
| 26- 1 | 21 | 34 | 6 | 24 | 8 | 32 | 32 | 59 | .. | .. | 21 | 40 | 61 | 86 | .. | .. |
| 26- 2 | 0 | 16 | 0 | 15 | 0 | 13 | 11 | 28 | 12 | 30 | 18 | 44 | 23 | 50 | 24 | 50 |
| 26- 3 | 12 | 33 | 14 | 40 | 20 | 51 | 12 | 37 | 43 | 71 | 23 | 47 | 21 | 43 | .. | .. |
| 26- 5 | 19 | 41 | 34 | 52 | 58 | 76 | 42 | 70 | 52 | 71 | 21 | 42 | 7 | 17 | 7 | 19 |
| 26- 6 | 6 | 11 | 7 | 22 | 21 | 44 | 28 | 60 | 56 | 85 | 37 | 63 | 40 | 61 | 40 | 60 |
| 26- 7 | 11 | 33 | 8 | 28 | 16 | 50 | 13 | 50 | 27 | 71 | 29 | 78 | 32 | 78 | 32 | 78 |
| 26- 9 | 0 | 14 | 0 | 17 | 5 | 23 | 0 | 20 | 0 | 28 | 11 | 35 | 29 | 58 | 27 | 54 |
| 26-10 | 31 | 45 | 10 | 27 | 7 | 25 | 4 | 26 | 2 | 28 | 0 | 30 | 0 | 22 | 0 | 23 |
| 26-11 | 13 | 33 | 0 | 22 | 4 | 27 | 12 | 31 | 41 | 75 | 40 | 76 | 45 | 79 | 46 | 77 |
| 26-12 | 0 | 14 | 0 | 11 | 0 | 12 | 0 | 26 | 0 | 15 | 0 | 12 | 0 | 12 | 0 | 13 |
| 26-13 | 0 | 11 | 4 | 27 | 22 | 44 | 30 | 58 | 48 | 77 | 31 | 58 | 28 | 56 | 39 | 69 |
| 26-15 | 0 | 17 | 0 | 16 | 4 | 16 | 18 | 41 | 25 | 44 | 23 | 41 | 13 | 32 | 0 | 16 |
| 26-16 | 0 | 31 | 0 | 11 | 0 | 11 | 0 | 14 | 4 | 17 | 5 | 20 | 3 | 18 | 0 | 17 |
| 26-17 | 28 | 50 | 55 | 70 | 45 | 66 | 43 | 68 | 37 | 63 | 40 | 64 | 41 | 67 | 42 | 72 |
| 26-19 | 25 | 51 | 16 | 39 | 12 | 47 | 19 | 41 | 20 | 48 | 21 | 49 | 25 | 51 | 24 | 54 |
| 26-31 | 10 | 29 | 8 | 25 | 20 | 42 | 50 | 71 | 57 | 83 | 59 | 80 | 46 | 66 | 24 | 39 |
| 26-22 | 47 | 75 | 47 | 70 | 52 | 77 | 53 | 81 | 48 | 84 | 57 | 90 | 60 | 93 | 60 | 94 |
| 26-24 | 24 | 75 | 18 | 78 | 41 | 67 | 50 | 74 | 38 | 56 | 13 | 42 | 11 | 26 | 16 | 30 |
| Average | 13.7 | 34.0 | 12.6 | 33.0 | 18.6 | 40.1 | 23.1 | 47.5 | 30.0 | 55.6 | 24.6 | 50.5 | 26.9 | 50.8 | 23.8 | 47.8 |

tion we could as to the movements of the stomach and the speed of passage of the barium along the gastro-intestinal tract. The results obtained showed that in the sixteen patients there was but one with definite ptosis of the stomach; this patient also showed marked atony. He also failed to show the presence of any free hydrochloric acid when subjected to the fractional test meal. Five cases exhibited hyperperistalsis and three hypoperistalsis, the peristaltic movements in the other cases being normal. Five cases showed slight atony of the muscular wall. Not any of the cases showed the presence of any organic lesion, the conus being normal and pylorospasm absent. In three cases, the barium failed to reach the ileocecal valve during the six hours following the ingestion of the barium. In one of the remaining thirteen cases, the barium had reached the hepatic flexure and in two the splenic flexure;

in the rest, it was found in the cecum at the end of six hours. In these studies there was again no correlation in the behavior of the gastrointestinal tract and the length of addiction or the amount of drug used by the different patients in a twenty-four hour period.

LIVER

The phenoltetrachlorphthalein test of the function of the liver as devised by Rosenthal [2] was carried out in ten different addicts. In eight of the ten, the dye disappeared from the blood stream in less than one hour, the normal time of disappearance. At the end of one hour, there

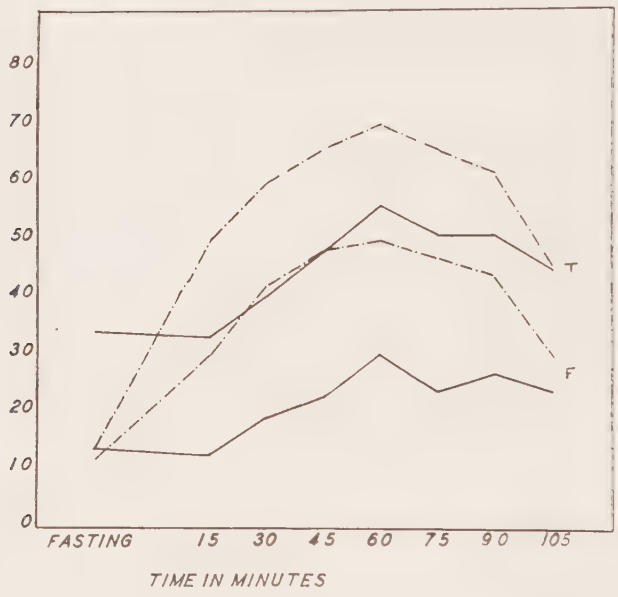


Chart 1.—Average response to a standard test meal of the gastric secretion of a group of human addicts receiving morphine, compared to the normal isotrophic curve of Rehfuss. *T* indicates total acid and *F*, free hydrochloric acid. In this chart and in charts 2 and 3, the solid line indicates addicts and the broken line, normal persons.

was still 3 per cent left in one case, and 0.9 per cent in the other. At the end of two hours, one case still showed the presence of 1 per cent of the dye. Van den Bergh's test [3] was negative in nine cases studied. The icterus index of the serum showed an average of 5.2 and varied

2. Rosenthal, S. M.: New Method of Testing Liver Function with Phenoltetrachlorphthalein, J. Pharm. & Exper. Therap. **23**:385 (June 5) 1924.

3. Van den Bergh, quoted by McNee, J. W.: Jaundice: Review of Recent Work, Quart. J. Med. **16**:390 (July) 1923.

from 3 to 9 in ten cases studied. The average normal of this test as devised by Murphy [4] is given as from 4 to 6.

### DEXTROSE TOLERANCE TEST

Ten different addicts were selected to determine the rapidity of rise and fall of dextrose in the blood following its ingestion by mouth. Each addict was given 1.75 Gm. of dextrose per kilogram of body weight. The average results obtained are found in table 2 and are plotted in chart 2, which also contains a normal curve. The peak of the curve is reached at the end of an hour, and the curve is still elevated at the end of two hours as compared to the normal curve shown for and derived from normal patients in the Philadelphia General Hospital. A study of the individual cases shows a striking uniformity of the curve in all but two of the cases. In one of these, the blood sugar rose to 170 mg. per hundred cubic centimeters of blood at the end of one hour, while the

TABLE 2.—*Results of Phenoltetrachlorphthalein, van den Bergh, Icterus Index and Dextrose Tolerance Tests in Human Addicts During the Administration of Morphine*

| | Phenoltetrachlorphthalein | | | Van den Bergh | Icterus Index | Dextrose Tolerance, Mg. per 100 Cc. of Blood | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 15 Min. | 1 Hour | 2 Hours | | | Fasting | 15 Min. | 1 Hour | 2 Hours |
| Number of cases | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 10 | 10 |
| Highest | 8% | 3% | 1% | .. | 9 | 120 | 128 | 170 | 157 |
| Lowest | 4% | 0% | 0% | .. | 3 | 96 | 102 | 98 | 101 |
| Average | 5.8% | 0.9% | 0% | Negative | 5.2 | 107 | 121 | 130 | 127 |

other reached its peak of 157 mg. only at the end of two hours. One case studied showed a decided decline in blood sugar of from 128 to 98 mg. in the period of fifteen minutes and one hour after the dextrose was given. The dosage administered to these addicts ranged from 5 to 16 grains (0.32 to 1.04 Gm.) of morphine sulphate in a period of twenty-four hours with no correlation between the amount of the drug and differences in the results.

### KIDNEY

The urines of 100 addicts were subjected to the usual chemical and microscopic examination. All specimens examined were taken from the first urine passed in the morning before breakfast. The specific gravity varied from 1.014 to 1.035, the average for the 100 cases being 1.022 with nothing significant in the color. Sugar, as determined by Benedict's method, was not found in a single case. Seventeen of the 100 cases showed from a faint trace to a trace of albumin. Of these seventeen

4. Murphy, William P.: Biliary System Functional Tests, Arch. Int. Med. **37**:797 (June) 1926.

cases, only four showed the presence of a few hyaline casts. In eighteen cases there was an excess of leukocytes, while in one case a few red blood cells were found.

The phenolsulphonphthalein test of kidney function, in which the dye was injected into the lumbar muscles, was carried out in twenty different addicts. The average elimination of the dye was 56 per cent in two hours, the average for the first hour being 42 per cent and for the second hour, 14 per cent. The lowest elimination found was 22 per cent in the first hour and 10 per cent in the second hour. The urine of this addict was free from albumin and sugar, and the blood urea nitrogen was 12 mg. per hundred cubic centimeters of blood. The most rapid elimination found was 52 per cent in the first hour and 22 per cent in the second, or a total of 74 per cent in two hours. Five of the cases showed

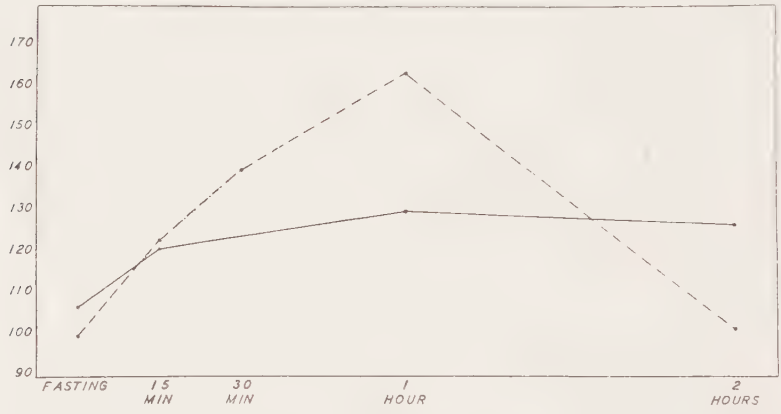


Chart 2.—Average blood sugar response to the ingestion of 1.75 Gm. of dextrose per kilogram in a group of human addicts receiving morphine, compared to a series of normal persons.

an elimination of less than 50 per cent in two hours. All cases studied showed the greatest percentage of excretion in the first hour.

Six cases were selected and studied in which the total intake of food and water was limited to the same amount and character and given at the same period of the day. The same procedure was also carried out in three normal nonaddicts. The total quantity of urine excreted in twenty-four hours compared favorably with the total quantity excreted by the normal patients.

## BASAL METABOLISM

Sixty-eight determinations of the basal metabolic rate were made on twenty-five different addicts. A number of additional determinations had to be discarded on account of obvious poor cooperation on the part of the patient. Prof. August Krogh's basal metabolism recording

apparatus was used for this work. The accuracy of this apparatus was checked several times a week with a person whose metabolism was known to be normal. The number of determinations accepted for each person varied from a single determination to as high as four in several cases. The majority, however, were always studied until at least two determinations were obtained on separate days. The oxygen consumption was studied over a period of ten minute intervals.

Table 3 has been arranged in order to show the variations of the metabolism according to the amount of drug used in a twenty-four hour period. It will be noted that with the exception of the persons using more than 20 grains (1.3 Gm.) in a twenty-four hour period and the two using less than 4 grains (0.26 Gm.) in the same period, the extremes obtained above and below normal are practically the same, namely, — 28

TABLE 3.—*Basal Metabolic Rate of Twenty-Five Addicts Grouped According to the Amount of Morphine Used Per Twenty-Four Hours*

| | Amount of Drug Used in 24 Hours | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 to 4 Grains | | 5 to 9 Grains | | 10 to 14 Grains | | 15 to 19 Grains | | 20 to 24 Grains | |
| Basal metabolic results | 18 to 33 | | −14 to 10 | | − 7 to 12 | | − 5 to −16 | | −10 to −13 | |
| | −14 to 4 | | − 3 to −22 | | 9 to 15 | | 3 to 6 | | −14 to −25 | |
| | | | −11 to 16 | | −12 to −28 | | −15 to 9 | | | |
| | | | −13 to 2 | | − 1 to 11 | | 5 to 8 | | | |
| | | | 8 | | 9 to −26 | | 14 | | | |
| | | | | | − 6 to 8 | | | | | |
| | | | | | 13 to 6 | | | | | |
| | | | | | 24 | | | | | |
| | | | | | 20 | | | | | |
| | | | | | 4 | | | | | |
| | | | | | 5 | | | | | |

per cent and + 24 per cent. Both persons using more than 20 grains of morphine a day showed decreases in the basal metabolism ranging from — 10 per cent to — 13 per cent and — 14 per cent to — 25 per cent, respectively. One of the patients using only 4 grains daily had the greatest increase, namely, + 33 per cent. The cooperation at both extremes seemed to be excellent; yet we are inclined to the belief that when large quantities of the drug were used, there was considerably less nervousness than in the case in which only 4 grains were used in the twenty-four hour period.

The average variation of the entire group of sixty-eight determinations ranged from — 12 per cent to + 11 per cent, which compares favorably with the normal variation of from — 10 per cent to + 10 per cent. Thirteen of the thirty-nine results obtained in which the metabolism was found to be decreased were lower than the average low of — 12 per cent, and fourteen of the twenty-nine results obtained in which the figures ranged in the positive direction were above 12 per cent.

### TEMPERATURE

The average temperature taken with the thermometer in the closed mouth underneath the tongue in 100 cases was found to be 98.3 F. The highest temperature reported was 98.9 and the lowest, 97.8. The rectal temperature taken in ten cases varied from 98 to 99.6, with an average of 99.2. All patients selected were free from abscesses and intercurrent infection.

### THE EFFECT OF A SINGLE DOSE OF MORPHINE ON THE BLOOD SUGAR OF THE ADDICT

Six addicts were selected from whom blood was drawn in the morning prior to the time at which the first regular injection of morphine was due. They were then given their regular dosages, and samples of blood were taken at intervals of fifteen minutes, thirty minutes, one hour, one and a half hours and two hours following the injection. The samples of blood were analyzed for sugar content. Table 4 gives the average results

TABLE 4.—*Average Response of the Blood Sugar in Human Addicts to a Single Dose of Morphine*

| Number of Cases | Basal | After Injection | | | | |
|---|---|---|---|---|---|---|
| | | 15 Minutes | 30 Minutes | 1 Hour | 1½ Hours | 2 Hours |
| 6 | 84 mg.* | 89 mg. | 93 mg. | 92 mg. | 95 mg. | 93 mg. |

* Milligrams per hundred cubic centimeters of blood.

obtained, showing the effects to be negligible, the slight rise present being within the limit of error of the method used [5] for analysis. Two additional cases were selected and the same procedure followed except that the dosage given was double the amount that would have been given ordinarily. The results obtained in these two cases were identical with those obtained in the six cases in which the normal dosage was given, namely, an insignificant rise in the quantity of sugar present in the circulating blood.

### THE EFFECT OF EPINEPHRINE ON THE BLOOD SUGAR OF ADDICTS COMPARED TO ITS EFFECT ON THAT OF NORMAL PERSONS

Five addicts were selected in order to determine the degree of response in the rise of the blood sugar to a standard injection of epinephrine, namely, 0.001 Gm. of epinephrine hydrochloride. In order to obtain a comparison, the same solution was used in five normal persons.

5. Folin, Otto; and Wu, Hsien: A Simplified and Improved Method for Determination of Sugar, J. Biol. Chem. **41**:367 (March) 1920.

Chart 3 shows a comparison of the relative rise of the blood sugar taken at fifteen minute, thirty minute, one hour, and two hour intervals. It will be noticed that the curves are practically identical, showing no difference in the response of the rise in sugar in addicts as compared to that of normal persons. The epinephrine was always given at an interval of fifteen minutes following the injection of the regular dosage of morphine sulphate. We have shown in the preceding paragraph that morphine per se does not cause a rise in blood sugar. The effect of the epinephrine on the blood pressure of both addicts and normal persons was measured, but wide fluctuations in both groups did not justify the drawing of any conclusions.

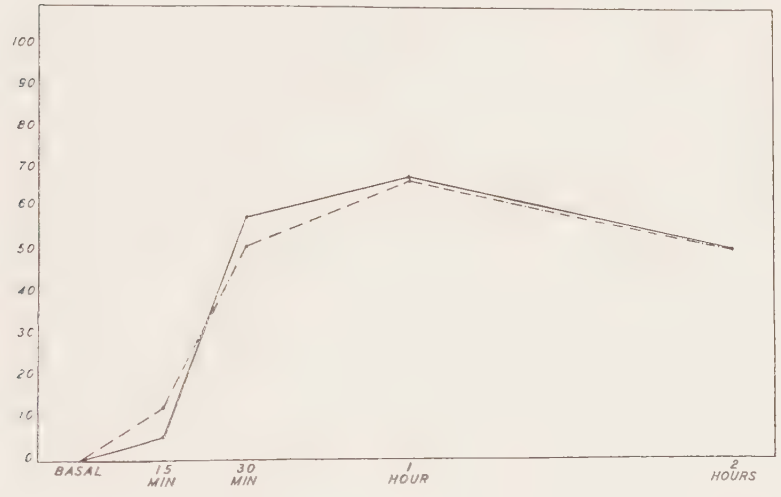


Chart 3.—Average blood sugar response to the injection of 1 cc. of epinephrine hydrochloride (1:1,000) in a series of human opium addicts receiving morphine, and in a group of normal persons.

## THYMUS

Roentgen studies to detect the presence of persistent thymus were made on ten addicts. The results in all cases studied were negative. From the clinical evidence there was no reason to suspect the presence of the thymus in any of our cases.

## COMMENT AND LITERATURE

The results obtained in our studies of the stomach by means of the x-ray and fractional analysis of the gastric juice indicate little change in the behavior of this organ as the result of prolonged usage of opium or

its derivatives. Sollier [6] asserted that not only does morphine stimulate the function of the gastric glands, but it also increases the tonicity of the stomach, and that as soon as the drug is withdrawn the stomach dilates. Morat [7] called attention to the markedly affected condition of the digestive tract, pointing out that the salivary secretion was much lessened, and that the gastric and intestinal glands suffered no less. Bishop [8] described the impaired digestion of addicts. The degree of atony present in four of our five cases was so slight as to demand little attention, so that only one of our sixteen cases showed any marked change in the muscular tone of the stomach. The same comment may be made concerning the peristaltic movements; in five cases a degree of hyperperistalsis and in three cases hypoperistalsis were present.

We do not believe that the secretion of the gastric juice is impaired to any great extent. There was a delay in four of the eighteen cases studied, and the average total response was less than the isotrophic response of Rehfuss.[1] Thirteen of our cases showed a normal response, the quantity secreted being well within the normal limits.

The rate of progression of the barium through the small intestine was decreased in three cases. This delay in movement is undoubtedly significant and may perhaps be attributed to the action of the drug, but it is not universally present, as in the other sixteen cases the movement of the barium was normal.

In 100 per cent of our cases in the ward daily evacuation of the bowels did not occur without the aid of a cathartic. This marked constipation is one of the few universally accepted characteristics of the behavior of the gastro-intestinal tract of addicts. We have had statements from addicts that their bowels move each day without the aid of cathartics or enemas, but in practically every case the movement was brought about because the addict refrained from the drug until a movement occurred. While the drug is being administered in the ward, we have always been forced to give relief in the form of medication or enemas.

The only manifestation that may be regarded as abnormal which we have been able to detect in the behavior of the kidney is that in seventeen of the 100 cases studied an amount of albumin ranging from a faint trace to a trace was found. Only four of these cases showed a

6. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine méd., 1894, pp. 146-152.

7. Morat, D.: Le sang et les sécrétions au cours de la morphinomanie et de la désintoxication, Paris, G. Steinheil, 1911, p. 180.

8. Bishop, E. S.: Narcotic Drug Problem; Pathology, Pathognosis and Treatment, Philadelphia, F. A. Davis and Company, 1913, p. 524.

few hyaline casts. This is in partial agreement with Levinstein [9] and Sollier,[6] who asserted that albuminuria was frequently present in opium addicts. Morat,[7] however, came to the conclusion that it was a common error to regard albuminuria as being present in morphinism. The impairment of the phenolsulphonphthalein excretion in only one case and possibly slight impairment in four cases does not point to serious impairment of the kidneys as ascertained by means of this test. Studies of water balance [10] convinced us that the amount of urine secreted by the kidneys of addicts compares favorably with that of normal persons, and we do not agree with Lambert [11] that the quantity of urine secreted becomes diminished after prolonged addiction. Addicts will perspire freely when using more or less than the necessary amount of the drug to prevent withdrawal symptoms, but when the drug is administered as we employed it in our water balance experiments, the ratio of fluid secreted by the kidney to the insensible loss is the same as in a normal person. The absence of the dextrose is in agreement with the normal blood sugar content and also rules out renal glycosuria.

Impairment of liver function in the addict is also practically negligible as measured by the phenoltetrachlorphthalein test of Rosenthal [2] as well as by the negative results of the icterus index and van den Bergh tests. Bell [12] claimed the presence of fatty degeneration of the liver, and Morat [7] and Sollier [6] often found tenderness over the liver and in many cases increase in its size. In addition to the results obtained by tests, we have shown that the liver in the addict still responds with a degree of glycogenolysis following the injection of epinephrine hydrochloride quite comparable to that in normal persons. The rate of both rise and fall of the blood sugar in the dextrose tolerance test is somewhat delayed and is of sufficient interest to commend further study. The injection of morphine per se does not bring about any rise in the blood sugar in addicts and is in agreement with the observations of Plant and Pierce,[13] who found that when addiction became established in dogs the ability of a single dose of morphine to bring about a response in blood sugar disappeared.

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9. Levinstein, E.: Die Morphiumsucht, translated by Charles Harrer, 1878.

10. IX: Water Balance Studies During the Administration and the Withdrawal of Morphine, p. 96.

11. Lambert, A.: Chapter in Osler and McCrae: Modern Medicine, Philadelphia, W. B. Saunders Company, 1914.

12. Bell, F. McKee: Morphinism and Morphinomania, New York M. J. **93**: 680, 1911.

13. Plant, O. H., and Pierce, I. H.: Studies in Chronic Morphine Poisoning in Dogs. III. The Blood Sugar During Tolerance and Withdrawal, J. Pharm. & Exper. Therap. **33**:371 (July) 1928.

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Conclusions as to the basal metabolism in opium addicts during the administration of a sufficient amount of the drug to supply their needs is rather difficult in view of our observations. The average of the sixty-three determinations on twenty-five different addicts falls within the normal range. Yet there are many individual determinations that will range above or below the high and low normal figures. Unfortunately, we have only two cases in which the amount of drugs taken during twenty-four hours was below 4 grains and only two in which the amount is more than 20 grains, while most of our determinations were made on addicts who needed between 5 and 20 grains a day. The cases in which both limits of dosage per day were given would suggest that using small dosages did not decrease the metabolism and, if anything, increased it, while the cases in which the large dosage was given exhibited a decrease in the metabolism. Undoubtedly we were dealing again with one of the most difficult phases of the problem of drug addiction, namely, the quantity required to prevent withdrawal symptoms and arrest the "nervousness" of which these unfortunate people complain and which we are not able to measure. We are quite certain from our experience that an additional amount of the drug beyond a certain required dosage brings about a state of both mental and physical relaxation which undoubtedly will bring metabolism to its basal level and perhaps lower. If, on the other hand, the quantity is insufficient even though the patient may relax and remain quiet during the actual determination, the emotional disturbances which these people undoubtedly have may increase the metabolic rate above the normal level. There was no correlation between the basal pulse rates and the level of the metabolic rate.

## CONCLUSIONS

Studies of the stomach, kidney, liver, basal metabolism, thymus, temperature, dextrose response to epinephrine and dextrose response to morphine revealed no fundamental differences from normal in addicts to whom morphine was administered to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism, although the average metabolic rate was within normal limits. A delay in the return of the blood sugar to normal following the ingestion of dextrose given by mouth was also noted.

# VI. THE EFFECTS OF ABRUPT WITHDRAWAL FOLLOWED BY READMINISTRATION OF MORPHINE IN HUMAN ADDICTS, WITH SPECIAL REFERENCE TO THE COMPOSITION OF THE BLOOD, THE CIRCULATION AND THE METABOLISM

Continuing our studies on a series of male opium addicts, we wish to report the results obtained when the morphine administered to supply the patients' needs was abruptly withdrawn. These results include studies made at three hour intervals for a twenty-four hour period following the last administration of morphine and another series of results obtained when the drug had been stopped for forty-eight hours. Following the studies at the close of the forty-eight hour period, morphine was again administered to allay all suffering and again the same observations and studies were made.

## EXPERIMENTAL PROCEDURE

Two separate methods of approach were used in the study of changes brought about by the abrupt withdrawal of morphine which was being administered to supply the addict's need. One group was studied at intervals of three hours following the last administration of the drug; in four cases the studies were carried over a period of twenty-four hours. Another group of ten patients was studied immediately following the administration of the regular scheduled dosage, and the studies were then discontinued except for observations on the behavior until the end of a forty-eight hour withdrawal period, when the same studies were again made just before and after morphine was given again to allay all symptoms.

Only four of the eight patients selected in the first group were studied over periods of three hour intervals for twenty-four hours. The behavior and cooperation of the others were not conducive to accurate observations. No food was given during this period. The addicts were always required to remain in bed for a period of one-half hour before any studies were made.

Figures showing the pulse and respiration rates are the average of a five minute count. The figures for the blood pressure were obtained from as many patients as it was possible to measure the blood pressure of accurately within a five minute period, followed by a record of temperatures taken both by mouth and by rectum. When these observations were finished the basal metabolic rate was determined with Krogh's apparatus for recording basal metabolism, following which a sample of blood was drawn from a vein at the elbow. At the end of each period, the subject passed a sample of urine.

The procedure in the study of the group in which the drug was abruptly withdrawn for a period of forty-eight hours was quite similar. Following the administration of the last regular scheduled amount of morphine in the morning, the subjects immediately reclined in bed without breakfast and observations were made on circulation and respiration, and a sample of blood was taken after a rest period of half an hour. The subjects then resumed the standing position for a period of five minutes, and observations were made. A sample of blood was taken for analysis, and following this the addicts were subjected to the staircase climbing test which we have described in detail in another paper.[1] Except for observations concerning their conduct and remarks, further studies were not made until the completion of the withdrawal period. Food was allowed during the first thirty-six hours of this period, but in no cases was any taken at the expiration of the first twenty-four hours. At the end of the withdrawal period the addicts were again requested to recline, and the same observations were conducted: blood was drawn and the staircase climbing tests were again carried out.

With the completion of these observations and studies, the addicts were given sufficient morphine to supply their needs. As soon as they professed to feel normal the same studies, including the drawing of the blood and the staircase climbing tests, were again carried out.

## RESULTS

In table 1 we have tabulated the highest, lowest and average figures of the determinations and observations, together with the number of cases studied at three hour intervals for a period of twenty-four hours following the abrupt withdrawal of morphine. The word "basal" in the table indicates the results obtained immediately following the last injection.

There was a slight average rise in the pulse rate and a slight fall in the systolic pressure. The average red blood cell count remained practically the same with a slight increase in the hemoglobin. A slight average increase in the white cells appeared, with a relative increase of polymorphonuclear cells and a decrease in the lymphocytes. Physical and chemical studies of the blood did not reveal any significant changes except for a slight fall in two cases in which the amount of magnesium present was determined and a slight rise in the conductivity of the serum found. A slight rise in the temperatures both by mouth and by rectum was noted. The average figure for basal metabolism shows a definite increase from +6 to +22. The cooperation of the patients, however, at the end of the twenty-four hour period was obviously not

1. III: The Circulation and Respiration of Human Addicts During the Administration of Morphine, p. 21.

TABLE 1.—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine*

| | | Basal | 3d Hour | 6th Hour | 9th Hour | 12th Hour | 15th Hour | 18th Hour | 21st Hour | 24th Hour |
|---|---|---|---|---|---|---|---|---|---|---|
| Pulse | No. cases | 8 | 8 | 8 | 5 | 5 | 5 | 4 | 4 | 4 |
| | Highest | 80 | 76 | 78 | 76 | 74 | 73 | 75 | 78 | 80 |
| | Lowest | 58 | 57 | 53 | 51 | 55 | 63 | 60 | 57 | 67 |
| | Average | 68 | 62 | 64 | 68 | 64 | 66 | 69 | 70 | 74 |
| Blood pressure while reclining | No. cases | 8 | 8 | 8 | 5 | 5 | 5 | 4 | 4 | 4 |
| | Highest | 125/84 | 119/79 | 120/84 | 130/78 | 130/85 | 135/82 | 118/71 | 112/69 | 118/72 |
| | Lowest | 103/65 | 105/60 | 103/61 | 107/60 | 104/61 | 108/63 | 104/59 | 101/58 | 106/66 |
| | Average | 116/74 | 114/70 | 114/71 | 116/69 | 112/70 | 118/71 | 110/67 | 107/65 | 112/69 |
| Respirations | No. cases | 8 | 8 | 8 | 5 | 5 | 5 | 4 | 4 | 4 |
| | Highest | 18 | 15 | 15 | 23 | 22 | 18 | 16 | 16 | 15 |
| | Lowest | 11 | 11 | 10 | 12 | 11 | 12 | 9 | 9 | 10 |
| | Average | 14 | 13 | 13 | 17 | 15 | 15 | 13 | 12 | 13 |
| Temperature by mouth | No. cases | 8 | 8 | 8 | 5 | 5 | 5 | 4 | 4 | 4 |
| | Highest | 98.8 | 98.7 | 98.7 | 99.0 | 99.1 | 99.4 | 99.0 | 99.6 | 101.1 |
| | Lowest | 97.3 | 97.6 | 97.2 | 98.1 | 98.4 | 98.5 | 98.6 | 98.8 | 99.2 |
| | Average | 98.4 | 98.4 | 98.2 | 98.5 | 98.6 | 98.9 | 98.8 | 99.0 | 99.7 |
| Rectal temperature | No. cases | 8 | 8 | 8 | 5 | 5 | 5 | 4 | 4 | 4 |
| | Highest | 99.6 | 99.4 | 99.7 | 99.6 | 99.7 | 99.8 | 99.9 | 100.6 | 101.9 |
| | Lowest | 98.0 | 98.7 | 98.0 | 98.7 | 98.9 | 98.8 | 99.4 | 99.6 | 99.9 |
| | Average | 99.2 | 99.1 | 99.2 | 99.2 | 99.4 | 99.3 | 99.6 | 100.0 | 100.7 |
| Hemoglobin | No. cases | 8 | 8 | 6 | 3 | 4 | 4 | 4 | 4 | 4 |
| | Highest | 19.8 | 19.1 | 20.3 | 15.9 | 16.1 | 16.5 | 18.6 | 18.2 | 17.9 |
| | Lowest | 14.1 | 10.8 | 13.2 | 9.3 | 12.9 | 11.2 | 15.6 | 12.6 | 16.2 |
| | Average | 15.8 | 15.5 | 16.2 | 12.3 | 14.6 | 14.6 | 17.2 | 15.9 | 17.3 |
| Erythrocytes | No. cases | 8 | 8 | 7 | 5 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 4,940 | 5,000 | 5,080 | 4,865 | 4,740 | 4,870 | 5,010 | 5,360 | 5,050 |
| | Lowest | 3,850 | 3,910 | 3,850 | 3,910 | 4,530 | 4,660 | 4,280 | 4,240 | 4,100 |
| | Average | 4,527 | 4,506 | 4,517 | 4,521 | 4,490 | 4,718 | 4,547 | 4,747 | 4,515 |
| Leukocytes | No. cases | 8 | 8 | 7 | 5 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 15,400 | 14,600 | 15,600 | 9,400 | 8,860 | 11,200 | 11,400 | 11,500 | 12,900 |
| | Lowest | 4,000 | 5,000 | 7,800 | 7,300 | 7,000 | 7,200 | 10,400 | 10,400 | 9,000 |
| | Average | 8,980 | 9,888 | 10,771 | 8,020 | 7,800 | 9,700 | 10,925 | 10,825 | 11,125 |
| Polymorphonuclears | No. cases | 8 | 8 | 8 | 4 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 77 | 79 | 74 | 66 | 59 | 69 | 73 | 76 | 77 |
| | Lowest | 48 | 48 | 51 | 46 | 53 | 55 | 67 | 65 | 72 |
| | Average | 61 | 61 | 61 | 58 | 57 | 63 | 69 | 70 | 75 |
| Lymphocytes | No. cases | 8 | 8 | 8 | 4 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 46 | 44 | 45 | 42 | 41 | 39 | 27 | 30 | 24 |
| | Lowest | 19 | 18 | 19 | 28 | 34 | 24 | 23 | 19 | 18 |
| | Average | 33 | 33 | 33 | 34 | 36 | 30 | 25 | 24 | 20 |
| Large mononuclears | No. cases | 8 | 8 | 8 | 4 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 6 | 6 | 8 | 9 | 6 | 6 | 5 | 7 | 5 |
| | Lowest | 2 | 3 | 1 | 5 | 3 | 3 | 4 | 3 | 4 |
| | Average | 4½ | 4 | 4½ | 6 | 4 | 5 | 5 | 5 | 4½ |
| Eosinophils | No. cases | 8 | 8 | 8 | 4 | 3 | 5 | 4 | 4 | 4 |
| | Highest | 3 | 5 | 4 | 6 | 3 | 2 | 2 | 2 | 1 |
| | Lowest | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 0 |
| | Average | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 1 | ½ |
| Basophils | No. cases | 8 | 0 | 8 | 0 | 3 | 0 | 0 | 0 | 0 |
| | Highest | 2 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 0 |
| | Lowest | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Average | ½ | 0 | ½ | 0 | 1 | 0 | 0 | 0 | 0 |
| Urea | No. cases | 4 | 4 | 4 | 2 | 2 | 2 | 4 | 4 | 4 |
| | Highest | 12 | 13 | 13 | 10 | 10 | 10 | 15 | 13 | 17 |
| | Lowest | 8 | 8 | 9 | 10 | 9 | 8 | 10 | 10 | 9 |
| | Average | 10 | 10 | 11 | 10 | 9.5 | 9 | 11.5 | 11 | 11.5 |
| Sugar | No. cases | 8 | 8 | 8 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Highest | 107 | 111 | 115 | 107 | 93 | 100 | 107 | 111 | 109 |
| | Lowest | 69 | 83 | 78 | 63 | 69 | 76 | 89 | 89 | 100 |
| | Average | 86 | 94 | 91 | 84 | 81 | 86 | 91 | 100 | 105 |
| Creatinine | No. cases | 4 | 4 | 4 | 2 | 2 | 2 | 4 | 4 | 4 |
| | Highest | 1.25 | 1.31 | 1.29 | 1.12 | 1.08 | 1.12 | 1.55 | 1.58 | 1.5 |
| | Lowest | 1.085 | 1.145 | 1.11 | 1.05 | 1.07 | 1.18 | 1.03 | 1.07 | 1.08 |
| | Average | 1.145 | 1.24 | 1.17 | 1.08 | 1.075 | 1.19 | 1.28 | 1.32 | 1.28 |

TABLE 1.—*Studies of Human Opium Addicts at Three Hour Intervals for a Period of Twenty-Four Hours Following the Withdrawal of Morphine—Continued*

| | | Basal | 3d Hour | 6th Hour | 9th Hour | 12th Hour | 15th Hour | 18th Hour | 21st Hour | 24th Hour |
|---|---|---|---|---|---|---|---|---|---|---|
| Calcium | No. cases | 4 | 4 | 4 | 2 | 2 | 2 | 4 | 3 | 4 |
| | Highest | 10.46 | 10.97 | 10.82 | 10.50 | 10.8 | 10.4 | 10.48 | 10.38 | 11.63 |
| | Lowest | 9.84 | 9.23 | 9.12 | 9.03 | 9.45 | 9.63 | 9.99 | 6.53 | 9.90 |
| | Average | 10.15 | 10.22 | 9.99 | 9.76 | 10.12 | 10.01 | 10.19 | 8.47 | 10.72 |
| Magnesium | No. cases | 2 | 2 | .... | .... | .... | .... | 3 | 3 | 3 |
| | Highest | 2.12 | 2.08 | .... | .... | .... | .... | 1.84 | 1.98 | 1.80 |
| | Lowest | 2.06 | 2.0 | .... | .... | .... | .... | 1.64 | 1.46 | 1.50 |
| | Average | 2.09 | 2.04 | .... | .... | .... | .... | 1.75 | 1.64 | 1.61 |
| Specific gravity—plasma | No. cases | 8 | 6 | 8 | 4 | 3 | 4 | 4 | 3 | 4 |
| | Highest | 1.0282 | 1.0277 | 1.0296 | 1.0287 | 1.0281 | 1.0284 | 1.0283 | 1.0287 | 1.02931 |
| | Lowest | 1.0238 | 1.0238 | 1.0238 | 1.0239 | 1.0243 | 1.0239 | 1.0247 | 1.0249 | 1.02576 |
| | Average | 1.0261 | 1.0256 | 1.0263 | 1.0263 | 1.0257 | 1.0264 | 1.0261 | 1.0262 | 1.02687 |
| Protein, per cent | No. cases | 8 | 7 | 8 | 4 | 3 | 4 | 4 | 4 | 4 |
| | Highest | 8.32 | 9 | 9.28 | 8.66 | 8.31 | 8.66 | 8.25 | 8.60 | 8.77 |
| | Lowest | 6.91 | 6 | 6.57 | 6.51 | 6.62 | 6.57 | 7.09 | 7.03 | 7.03 |
| | Average | 7.81 | 7.65 | 7.86 | 7.85 | 7.58 | 7.88 | 7.65 | 7.80 | 7.94 |
| Conductivity | No. cases | 8 | 7 | 8 | 4 | 3 | 4 | 4 | 4 | 4 |
| | Highest | 143 | 148 | 139.2 | 139 | 137.6 | 137.2 | 147.0 | 144.4 | 147.0 |
| | Lowest | 130 | 133 | 133.6 | 136 | 133.0 | 135.0 | 142.6 | 138.4 | 140.2 |
| | Average | 136.1 | 137.6 | 135.4 | 137.2 | 135.4 | 136.0 | 144.1 | 142.4 | 143.3 |
| Basal metabolism | No. cases | 6 | 6 | 6 | 4 | 3 | 3 | 4 | 4 | 4 |
| | Highest | 20 | 14 | 19 | 11 | 6 | 24 | 14 | 14 | 36 |
| | Lowest | —6 | —12 | 2 | 6 | —1 | 8 | —9 | —9 | 12 |
| | Average | 6 | 2 | 8 | 8 | 2 | 14 | 5 | 5 | 22 |

as good as when determinations were made following the last administration of the drug. Chemical and microscopic examination of the urine in the cases in which the drug was abruptly withdrawn failed to reveal the appearance of albumin or casts as well as any other positive signs. It was noted that the color of the blood drawn from the same vein without stasis in the same persons at three hour intervals varied considerably. If the addict complained of feeling hot, the blood flowing into the collecting tube was bright red, suggesting a high percentage saturation of oxygen. On the other hand, if the addict complained of feeling chilly at the time, the blood was much darker in color, leading one to the belief that there existed a low percentage saturation of oxygen.

The physical changes noted in the addicts as the studies were carried on varied considerably. In the four cases in which the proposed twenty-four hour period of withdrawal was carried to completion the patients gave the observers the impression that they were suffering with a common cold in the head, lacrimation, sneezing and difficulty in breathing through the nostrils. Yawning was also present in these four cases, although it was not frequent. Dilatation of the pupils began between the sixth and ninth hour interval, in all cases. The patients complained of chills and exhibited the characteristic pilomotor activity of the skin known as "cold turkey" at the end of eighteen hours. Four showed slight muscular twitchings at the end of sixteen hours. None of the patients vomited, although at the end of the twenty-four hour period two complained of a serious gnawing sensation in the stomach

which they interpreted as the need for the drug. Three addicts had a bowel movement at the end of the eighteen hour period without the aid of medication, something unusual with them while taking drugs at regular intervals. At the end of the twenty-four hours, two of the addicts showed a decided change in disposition, becoming extremely surly and repeatedly stating that they hoped we would stop our "foolishness" and give them their drug. At the end of eighteen hours, one patient was seized with a spell of laughter sufficient to produce severe lacrimation. He expresed his condition as a "laughing yen."

The results obtained during comparative studies following the last administration, at the end of the forty-eight hour withdrawal period and following the readministration of the drug, are tabulated in table 2, and the results of the staircase climbing tests in table 3. Chart 1 shows graphically a comparison of the results of the staircase climbing tests obtained during the three different phases of study.

The most significant positive observations in these studies were a definite increase in the number of white cells with a relative increase in the polymorphonuclear cells and a decrease in the lymphocytes at the end of the withdrawal period. Following the readministration of the drug, there was still a slightly further average increase in the number of white cells. Two cases, however, failed to show any increase in the number of white cells. On the other hand, one of our cases showed an increase in the number of white cells of from 8,100 to 27,000 at the end of the forty-eight hour period and reached 31,000 one hour after the readministration of the drug when all the withdrawal symptoms had apparently disappeared. A count taken six hours later showed a still further increase to 34,000. Twenty-four hours after the readministration of the drug, they had fallen to 14,000. This addict required 10 grains (0.65 Gm.) of morphine a day, the same amount required by one of our patients whose leukocytes numbered 8,300 at the beginning of the withdrawal period and who had the insignificant rise to 8,500 at the end of the period. The two addicts who did not show a change in the number of leukocytes appeared to suffer as much as the other eight who showed definite increases.

The red blood cells were studied in only two cases and showed a slight rise after the abrupt withdrawal and a further slight increase following readministration of the drug in both cases. Determinations of hemoglobin by means of the Newcomer plate in ten cases showed an average rise of from 15.1 to 16.9 Gm., and in eight of these it remained practically the same after the readministration of the drug. The rise in hemoglobin occurred in all our cases as did the slight increase in the red cell volume following abrupt withdrawal.

The results obtained from the determination of the dry matter in the whole blood and plasma showed an average increased concentration of

TABLE 2.—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration*

| | | Before Abrupt Withdrawal | At End of 48 Hour Abrupt Withdrawal | After Readministration of Morphine at End of 48 Hour Withdrawal Period |
|---|---|---|---|---|
| Pulse rate while reclining | No. cases | 10 | 10 | 10 |
| | Highest | 80 | 71 | 83 |
| | Lowest | 52 | 50 | 54 |
| | Average | 64 | 61 | 69 |
| Pulse rate while standing | No. cases | 10 | 9 | 9 |
| | Highest | 112 | 112 | 123 |
| | Lowest | 59 | 73 | 88 |
| | Average | 79 | 93 | 107 |
| Blood pressure while reclining | No. cases | 10 | 10 | 10 |
| | Highest | 138/92 | 140/84 | 129/79 |
| | Lowest | 102/60 | 109/63 | 88/60 |
| | Average | 120/73 | 121/73 | 111/71 |
| Blood pressure while standing | No. cases | 10 | 9 | 9 |
| | Highest | 130/90 | 138/94 | 112/90 |
| | Lowest | 86/64 | 110/74 | 80/60 |
| | Average | 110/79 | 116/85 | 98/77 |
| Respiration | No. cases | 10 | 8 | 8 |
| | Highest | 22 | 24 | 34 |
| | Lowest | 12 | 11 | 12 |
| | Average | 17 | 16 | 17 |
| Hemoglobin | No. cases | 10 | 10 | 7 |
| | Highest | 16.7 | 18.9 | 18.1 |
| | Lowest | 13.2 | 14.8 | 13.8 |
| | Average | 15.1 | 16.9 | 15.6 |
| Erythrocytes | No. cases | 3 | 2 | 2 |
| | Highest | 4,827 | 5,150 | 5,550 |
| | Lowest | 4,450 | 4,300 | 4,500 |
| | Average | 4,609 | 4,700 | 5,025 |
| Leukocytes | No. cases | 9 | 9 | 8 |
| | Highest | 13,100 | 27,800 | 34,000 |
| | Lowest | 7,500 | 7,800 | 8,000 |
| | Average | 9,800 | 15,200 | 16,980 |
| Polymorphonuclears | No. cases | 7 | 9 | 7 |
| | Highest | 78 | 97 | 86 |
| | Lowest | 47 | 52 | 56 |
| | Average | 62 | 72 | 68 |
| Lymphocytes | No. cases | 7 | 9 | 7 |
| | Highest | 46 | 40 | 39 |
| | Lowest | 20 | 2 | 12 |
| | Average | 33 | 25 | 27 |
| Large mononuclears | No. cases | 7 | 9 | 7 |
| | Highest | 7 | 6 | 4 |
| | Lowest | 0 | 0 | 0 |
| | Average | 3 | 1 | 2 |
| Eosinophils | No. cases | 7 | 9 | 7 |
| | Highest | 2 | 2 | 3 |
| | Lowest | 0 | 0 | 0 |
| | Average | 1 | 1 | 2 |
| Basophils | No. cases | 7 | 9 | 7 |
| | Highest | 1 | 1 | 1 |
| | Lowest | 0 | 0 | 0 |
| | Average | 1 | 1 | 1 |
| Urea | No. cases | 3 | 4 | 5 |
| | Highest | 15 | 16 | 18 |
| | Lowest | 11 | 10 | 11 |
| | Average | 13 | 13 | 15 |
| Sugar | No. cases | 3 | 4 | 5 |
| | Highest | 101 | 115 | 126 |
| | Lowest | 69 | 85 | 93 |
| | Average | 93 | 101 | 107 |
| Cholesterol, whole blood | No. cases | 10 | 7 | 8 |
| | Highest | 215 | 235 | 250 |
| | Lowest | 163 | 175 | 150 |
| | Average | 189 | 208 | 189 |

TABLE 2.—*Studies of the Effect on Human Opium Addicts of the Abrupt Withdrawal of Morphine for a Period of Forty-Eight Hours and Its Readministration—Continued*

| | | Before Abrupt Withdrawal | At End of 48 Hour Abrupt Withdrawal | After Readministration of Morphine at End of 48 Hour Withdrawal Period |
|---|---|---|---|---|
| $p_H$ blood | No. cases | 3 | 4 | 4 |
| | Highest | 7.51 | 7.51 | 7.45 |
| | Lowest | 7.37 | 7.43 | 7.38 |
| | Average | 7.45 | 7.46 | 7.42 |
| Dry matter, whole blood | No. cases | 10 | 10 | 7 |
| | Highest | 22.7 | 24.5 | 23.3 |
| | Lowest | 20.1 | 21.7 | 16.2 |
| | Average | 20.7 | 22.6 | 21.9 |
| Dry matter, cells | No. cases | 6 | 9 | 8 |
| | Highest | 40.8 | 43.6 | 55.3 |
| | Lowest | 38.2 | 37.5 | 27.4 |
| | Average | 41.3 | 40.7 | 41.2 |
| Dry matter, plasma | No. cases | 10 | 10 | 8 |
| | Highest | 10.2 | 11.5 | 11.4 |
| | Lowest | 8.2 | 9.2 | 8.4 |
| | Average | 9.1 | 10.1 | 9.9 |
| Schneider's score | No. cases | 8 | 7 | 7 |
| | Highest | 15 | 12 | 11 |
| | Lowest | 1 | 9 | 1 |
| | Average | 10.4 | 10 | 4 |
| Oxygen percentage saturation of venous blood | No. cases | .. | 6 | 6 |
| | Highest | .. | 60.7 | 79.1 |
| | Lowest | .. | 39.3 | 49.2 |
| | Average | .. | 42.5 | 62.2 |
| Red cells, per cent by volume | No. cases | 6 | 10 | 7 |
| | Highest | 38.7 | 43 | 45.0 |
| | Lowest | 34 | 37.3 | 35.0 |
| | Average | 36.2 | 40.2 | 39.1 |

the blood of about 9 per cent. This tendency for a concentration was true in all the cases studied and following readministration of the drug did not return to the figure obtained before withdrawal. The dry matter of the cells remained unchanged.

Further studies showed no significant changes in the urea nitrogen, sugar and $p_H$ of the blood. A slight rise of the cholesterol of the whole blood was noted at the end of the abrupt withdrawal and a return to the same average figure following the readministration of the drug as that obtained before the withdrawal was begun. This rise of cholesterol was present in five of the seven cases studied.

In six cases studies of the percentage saturation of the venous blood drawn from the same vein at the elbow, following the abrupt withdrawal of the drug compared to the results obtained following the readministration of the drug, show an average increase in the percentage saturation of from 42.5 to 62.2 per cent. This rise in percentage saturation of the oxygen in the venous blood was present in all our cases.

The circulatory changes noted during these studies consisted in a slight fall of the average pulse rate while the patient was reclining during the abrupt withdrawal and a slight rise in the average rate

following the readministration of the drug. A study of the individual cases, however, shows this fall to be present in only six of the ten, the other four showing slight rises during the withdrawal period. The average rise of the pulse rate while the patient was reclining following the readministration of the drug occurred in nine of the ten cases, the other showing a slight fall in the rate.

The average pulse rate, determined while the patient was standing, increased fourteen beats per minute at the end of the forty-eight hour

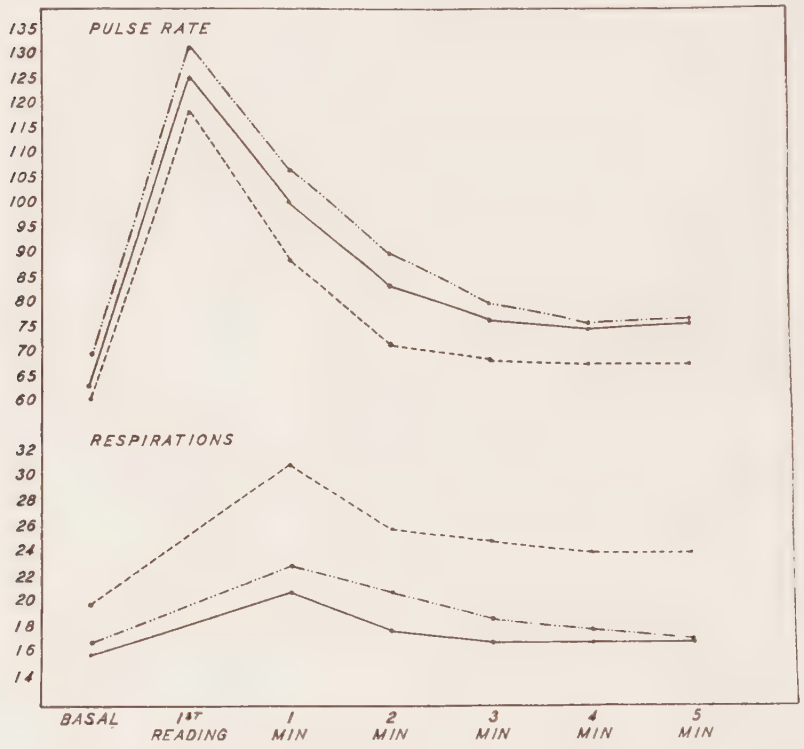


Chart 1.—Average changes in pulse and respiration rates in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period. In this chart and in chart 2, the solid line indicates, during administration; the broken line, after forty-eight hours, and the dash and dot line, following readministration.

period, with a further average increase of fourteen beats following the readministration of the drug. In all individual cases, the patients showed this increase of pulse rate while standing following withdrawal compared to the figure obtained at the beginning of this period as well as the further increase following the readministration of the drug.

No change was present in the average systolic pressure, taken while the patient was reclining, at the beginning of the withdrawal period as compared to that at the end of the period. Individual cases, however, showed some marked changes. In one case, the systolic pressure rose 37 mm. In another it fell 20 mm. The others showed rises and falls ranging from 2 to 7 mm. of mercury. An average rise of 6 mm. in the systolic pressure was noted when the figures for the average systolic pressure determined while the subject was standing, following the withdrawal period as compared with those obtained at the beginning of this period. An analysis of the individual cases shows that four of the ten exhibited this rise; in two the pressure remained the same and in three

TABLE 3.—*A Comparison of the Average Increase in the Pulse Rate, Respiration and Systolic Pressure and the Changes in Diastolic Pressure Following the Staircase Climbing Test on Human Opium Addicts Before Withdrawal, After a Forty-Eight Hour Period of Withdrawal of the Drug and Following the Readministration of Morphine*

| | 1st Reading | 1st Minute | 2d Minute | 3d Minute | 4th Minute | 5th Minute |
|---|---|---|---|---|---|---|
| Pulse (9 cases) | | | | | | |
| Before withdrawal | 62 | 37 | 20 | 13 | 11 | 12 |
| At end of withdrawal | 58 | 27 | 11 | 8 | 7 | 7 |
| Following readministration of drug | 62 | 37 | 20 | 10 | 16 | 7 |
| Respiration (9 cases) | | | | | | |
| Before withdrawal | .. | 5 | 2 | 1 | 1 | 1 |
| At end of withdrawal | .. | 11 | 6 | 5 | 4 | 4 |
| Following readministration of drug | .. | 6 | 4 | 2 | 1 | 0 |
| Systolic pressure (9 cases) | | | | | | |
| Before withdrawal | 29 | 30 | 25 | 16 | 9 | 4 |
| At end of withdrawal | 23 | 21 | 12 | 9 | 6 | 2 |
| Following readministration of drug | 18 | 19 | 15 | 13 | 8 | 4 |
| Diastolic pressure (9 cases) | | | | | | |
| Before withdrawal | —10 | —7 | —6 | —6 | —6 | —6 |
| At end of withdrawal | —6 | —4 | —2 | —3 | —0 | —2 |
| Following readministration of drug | —8 | —1 | 2 | 4 | 3 | 7 |

it showed a slight fall. An average fall in the systolic pressure taken while the patient was standing was noted in the ten cases following the readministration of the drug compared to the average systolic pressure, taken while the patient was reclining, at the beginning and end of this period. Seven of the ten cases showed this fall; in one the pressure remained the same and in the other two it showed slight rises. The greatest fall encountered was 23 mm.

Following the readministration of the drug, the systolic pressure taken while the subject was standing showed an average fall of 18 mm. compared to the average obtained at the end of forty-eight hours and 12 mm. compared to the average pressure at the beginning of the withdrawal period. Following the readministration of the drug, all cases without exception showed this fall in the systolic pressure while the patient was standing.

Schneider's test of physical fitness,[2] conducted in eight cases at the beginning of the withdrawal period, gave an average score of 10 points, the same as the average at the end of the forty-eight hour withdrawal period in seven cases. Following the readministration of the drug, the average score of the seven cases fell 6 points. This fall was directly due to the increase in the individual pulse rates and fall in the pressure when the subject changed from the reclining to the standing postures.

Studies of the staircase climbing test at the beginning and end of the forty-eight hour period and following the readministration of the drug do not reveal any great changes in the response of the circulatory system to this rather fatiguing test. If anything, the response fol-

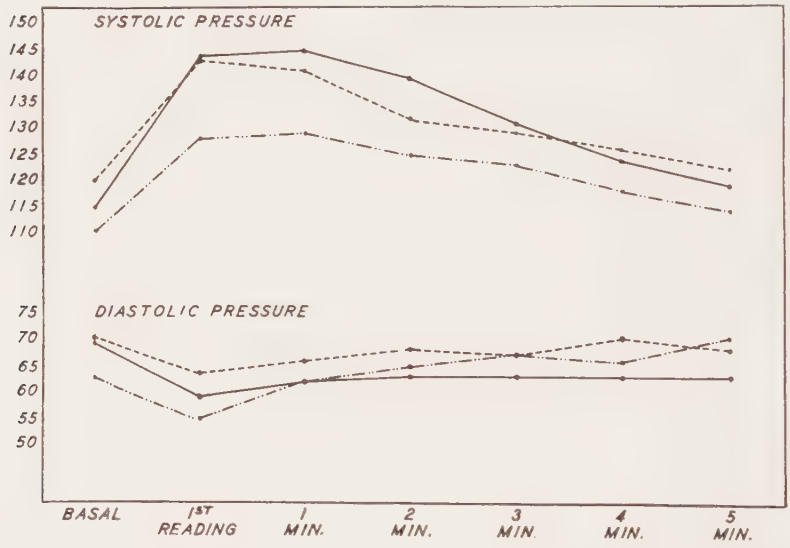


Chart 2.—Average changes in systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine, after withdrawal of morphine for forty-eight hours and following readministration of morphine after the forty-eight hour withdrawal period.

lowing the end of the forty-eight hour period when the addict complained of extreme muscular weakness was more similar to that of athletes than when the drug was being administered at regular intervals. The immediate increase in the respiratory rate at the close of the withdrawal period following the climbing of the staircase was the only indication of a poorer response to this test when compared to the test at the beginning of the period and following the readministration of the drug. The response following the readministration of the drug as

2. Schneider, E. C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

measured by the reaction of a trained person was poorer than when the addict was suffering, except the respiratory increase. We found that trained normal persons met the stress of climbing with the greatest rise in pressure and the least rise in pulse rate, and showed the quickest return to normal.[1]

No changes were noted in the respiratory rates while the patient was reclining either at the end of the forty-eight hours or following the readministration of the drug as compared to the figures obtained at the beginning of withdrawal. Individual cases also showed only small and insignificant changes, with the exception of one case in which the respirations were 17 at the beginning of withdrawal, 20 at the end of the withdrawal period and 34 following the readministration of the drug.

Only two of our cases showed a slight rise in temperature during this period. The highest temperature reached was 100.2 F.

Chemical and microscopic examination of the urine showed the presence of a trace of albumin in two cases, but neither one showed the presence of any casts. All other examinations of the urine gave negative results.

Attempts to determine the basal metabolism of the gastro-intestinal tract, gastric analysis, ingestion of barium for roentgenograms and dextrose for dextrose tolerance tests were futile, the cooperation of the patient being so poor as to cause us to abandon the attempts.

The general behavior and symptomatology of these addicts were uniform during the forty-eight hour withdrawal period. All cases showed the characteristic pilomotor activity and the lacrimation, sneezing and excessive yawning. Five of the ten patients vomited, and all had normal bowel movements at the end of twenty-four hours. Three developed diarrhea at the close of the forty-eight hour period. In four cases, sweating was marked, beginning at the end of thirty-six hours. Muscular twitching, particularly of the muscles of the face and extremities, was present in all cases. One of our patients had a violent twitching of the muscles of the left leg which he himself attempted to stop by improvising a tourniquet by means of a towel. At the close of the forty-eight hour period, one addict complained of diplopia, and on examination he had a definite weakness of the right external rectus muscle. The average weight lost by the ten addicts was 5¾ pounds (2.6 Kg.), the individual losses ranging from 4 to 8½ pounds (1.8 to 3.8 Kg.). The addicts presented a picture of dehydration; the features were drawn. The face, neck and upper anterior part of the chest had a peculiar color which we can describe best as a "dirty flush."

Not one of the addicts wished to continue the experiment following the twenty-four hour period, and the begging and pleading for morphine

for the following twenty-four hour period became extremely trying. Our judgment in selecting these addicts to act as subjects was based on their willingness to cooperate when requested to do so while the drug was being administered. This judgment proved to be poor, for those who offered the least resistance in persuasion turned out to be the most annoying at the end of the first twenty-four hours of the withdrawal period. One patient refused absolutely to continue at the end of thirty-six hours unless given a ¼ grain (16 mg.) of morphine to help him through the remaining twelve hours. He was given a hypodermic injection of sterile water and promptly went to sleep for a period of eight hours, with a tourniquet which he had improvised from a towel on his left leg to prevent muscular twitchings. He was awakened by the pain resulting from too tight application of the tourniquet. This addict never became aware of the fact that he was given nothing but sterile water. We wish to state, however, that such dramatic results with hypodermic injections of sterile water are rare; in most instances the addict cannot be fooled with this substitution, particularly following treatment.

While the studies were being conducted, changes for the better in disposition and disappearance of abjection could easily be noted at the end of the forty-eight hour withdrawal period just prior to the readministration of the drug. The anticipation of the morphine that was soon to be had seemed to have a distinctly beneficial action. A few minutes after the administration of the drug, all the addicts complained of a heavy feeling in the stomach; usually they also smiled and said that they were now experiencing the heavy sensation in the stomach that would bring relief. Despite the fact that within half an hour the addicts said that they felt normal and stronger than ever, the muscular twitchings about the face were still present in some cases. The patient who developed diplopia during the withdrawal period claimed to be entirely normal within forty minutes except that he was seeing double. Tests of the ocular movements revealed the presence of a weakness of the right external rectus muscle for several hours following the readministration of the drug.

We found the cessation of lacrimation, sneezing, yawning, pilomotor activity, muscular twitchings, the return of normal color to the face and the changes in disposition most striking following the readministration of the morphine.

## COMMENT AND LITERATURE

Our observations covering the abrupt withdrawal periods resulted in a failure to find any symptoms or signs that have as yet not been

described in the literature.[3] Our studies of the circulation, respiration and blood contribute nothing new, except for the discovery of a tendency toward a concentration of the blood and a slight rise in cholesterol during the abrupt withdrawal period. Morat [4] thoroughly described the appearance of leukocytosis at some time during the period of rapid withdrawal in a series of twenty-eight cases. Morat found this leukocytosis present in all his cases, whereas only eight of our ten cases showed it during the period of abrupt withdrawal. Studies of the blood of addicted dogs during withdrawal of the drug led Valenti [5] to the conclusion that vasoconstrictor substances were present in such blood, but this observation could not be confirmed by Pellini and Greenfield.[6] These authors were unable to detect any chemical changes in the blood of addicted dogs during the withdrawal stage. Plant and Pierce [7] found no change in the blood calcium of a dog who displayed violent symptoms during withdrawal of the drug.

We believe that our most important contribution to the study of withdrawal symptoms is the many negative observations obtained in these studies. This failure to find any marked changes, with the exceptions already mentioned, at the end of the withdrawal period as well as following the readministration of the drug, is open to criticism as we did not carry the experiments far enough. Our experience with these men at the end of a forty-eight hour period convinces us that such studies could be carried out only in institutions in which other methods than simple persuasion might be used.

The incessant begging and the annoying behavior of the addict during the withdrawal period becomes at times almost unbearable and may well react on the casual observer, so warping his judgment as to lead to conclusions that would not have been reached except for the behavior of the addict. Any one dealing with this group of people is fully aware

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3. Communication from G. H. Smith, Esq., to Dr. Johnson: On Opium Smoking Among the Chinese, Lancet **1**:707, 1841-1842. Levinstein, E.: Die Morphiumsucht, trans. by Charles Harrer, 1878. Sollier, P.: La demorphinisation et le traitement rationel de la morphinomanie, Semaine méd., 1894, p. 146. Bishop, E. S.: Narcotic Addiction, a Systemic Disease Condition, J. A. M. A. **60**:431 (Feb. 8) 1913.

4. Morat, D.: Le sang et les sécrétions au cours de la morphinomanie et de la désintoxication, Thèse de Paris, 1911.

5. Valenti, A.: Experimentelle Untersuchungen über den chronischen Morphinismus; Kreislaufstörungen hervorgerufen durch das Serum morphinisticher Tiere in der Abstinenzperiode, Arch. f. exper. Path. u. Pharmakol. **75**:437, 1914.

6. Pellini, E. J., and Greenfield, A. D.: Narcotic Drug Addiction: II. The Presence of Toxic Substance in the Blood Serum in Morphin Habituation, Arch. Int. Med. **33**:547 (May 15) 1924.

7. Plant, O. H., and Pierce, I. H.: Studies in Chronic Morphine Poisoning in Dogs: I. General Symptoms and Behavior During Addiction and Withdrawal, J. Pharmacol. & Exper. Therap. **33**:329 (July) 1928.

of the pernicious influence they exert. It has been our frequent experience to leave the wards with the firm conviction that these men are not organically sick, the whole picture being an emotional one, and that the viciousness attached to the picture could best be coped with in penal institutions. Just as frequently we have entered the ward and found these men suffering with violent muscular twitches, vomiting, perspiration and yawning and showing such a sickly appearance that we have been convinced that there must be an organic basis for their apparent suffering.

In favor of an emotional basis as a cause for the withdrawal symptoms, we wish to cite our negative observations. Despite the fact that the addicts claim to be so weak as to be scarcely able to move, their response to the staircase climbing test was carried out with the same efficiency as when drugs were administered, with the exception of the respiratory response; following the readministration of the drug, the response was, if anything, poorer. Such differences as exist in basal blood pressure, heart rate and respiratory rate are too small to indicate any significant change. Addicts will admit that when they are unable to obtain drugs and when withdrawal symptoms with extreme weakness have become severe, the assurance of an available supply at a considerable distance will cause them to travel this distance with remarkable speed and efficiency.

The concentration of the blood and loss of weight would indicate some organic disturbance, on the surface, but we believe that these two positive manifestations can be explained on the basis that the addicts will not take food or water and perspire to such an extent that they cannot help showing this loss of weight and the degree of concentration of blood found in our cases.

Yawning, restlessness, vomiting, diarrhea, perspiration and extreme weakness are found in many emotional states. This type of behavior has frequently been observed by one of us in a group of football players as well as in the coaching staff of a university football team just prior to the playing of a so-called "important game." Loss of appetite, marked restlessness, frequent yawning, diarrhea and, occasionally, vomiting constitute the picture. The players will state that they are so weak that they can scarcely move; yet, when the whistle starting the game is blown, all fatigue quickly disappears.

Further evidence that the picture of withdrawal symptoms has as its basis an emotional state is the response on the part of one of our addicts at the end of a thirty-six hour withdrawal period to the hypodermic injection of sterile water. Despite his obvious suffering, he immediately went to sleep and slept for eight hours. Addicts frequently speak about the "needle habit," in which the single prick of the needle brings about relief. It is not uncommon for one addict to give

another a hypodermic injection of sterile water and the recipient to derive a "kick" and become quiet. On the other hand, it has been our experience just as frequently to have the addict know that he was given a hypodermic injection of sterile water and to have him fail to respond to its effect. Paradoxic as it may seem, we believe that the greater the craving of the addict and the severity of the withdrawal symptoms the better are the chances of substituting a hypodermic injection of sterile water to obtain temporary relief.

The presence of diplopia, marked increase in the number of leukocytes and albuminuria constitute sufficient evidence for one to look on withdrawal symptoms as having a true organic basis. Leukocytosis has been described in emotional states, but the degree reached in some of our cases, in four the leukocyte count being over 20,000 and in one reaching 27,000, would make one proceed with caution in the diagnosis of a clinical case before attributing such a count to pure emotionalism. Recently, however, Garrey [8] and his co-workers were able to establish a mental condition which frequently brings about an increase of from 100 to 300 per cent in the number of leukocytes. It is the belief of these observers that they are dealing merely with a redistribution due to fluctuation in the capillary bed in which leukocytes are trapped in the nonfunctioning capillaries.

White cell counts on the football players already cited made daily for a week before an important game and just prior to the game when they were showing symptoms of yawning, diarrhea and restlessness and complaining of extreme weakness failed to show any change from the normal count.

Muscular twitches are, at times, of such magnitude as to preclude any possibility of pure nervousness. The presence of albumin in the urine, mentioned by other investigators but curiously absent in this series of cases studied, is further evidence of the organic nature of these disturbances.

Failure of disappearance of the leukocytosis, diplopia and muscular tremors following the readministration of morphine when relief was obtained by the addict are difficult to explain. To those who are inclined to accept an emotional basis as the cause of withdrawal symptoms, a satisfactory explanation would be that the craving for the drug brings about emotional states sufficiently powerful to cause organic changes and that readministration of the drug brings mental relief long before the resulting organic changes can rectify themselves. On the other hand, if some true organic disturbance is the basis of the suffering, the readministration of morphine brings about relief from the peripheral sensations just as morphine relieves the patient from the pain of cancer but not from the cancer itself.

8. Garrey, W. E.: Personal communication to the authors.

## CONCLUSIONS

Abrupt withdrawal of morphine for a period of twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied by negligible changes in the pulse rate, leukocyte count and basal metabolic rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

In ten addicts, abrupt withdrawal of morphine for a period of forty-eight hours resulted in the appearance of severe withdrawal symptoms. One case showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven of the ten cases. Albuminuria was found in two cases. The $p_H$ of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight occurred during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood remained for several hours, as did the diplopia and muscular twitchings of the face. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. The staircase climbing test and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period.

# VII. A COMPREHENSIVE STUDY OF EFFECTS OF THE SCOPOLAMINE TREATMENT FOR MORPHINE ADDICTION

The routine treatment that we have employed in the Philadelphia General Hospital has been confined chiefly to the scopolamine method. We have made studies of the addicts before treatment was begun and at intervals of from two to four days following the apparent cessation of the withdrawal symptoms, which were universally present while the patients were under the influence of scopolamine. During the latter study period, we encountered all grades of behavior and appearances of illness. We wish to report in this paper comparative studies made while morphine was being administered to supply the needs of the addict and again following the cessation of mental confusion produced by scopolamine. These studies include those of the heart and circulation, physical and chemical properties of the blood, metabolism, temperature, changes in weight, vital capacities, the urine, functional tests of the kidney and liver, and reaction to epinephrine and to atropine.

## METHOD OF TREATMENT

The routine method of treatment, which was carried out in a more or less uniform manner, is as follows: During the first twenty-four hours following admission, the patient is given morphine sulphate hypodermically in sufficient quantities to prevent withdrawal symptoms. If no studies during the administration of morphine are contemplated, he is placed on a liquid diet for this period. At the same time he is given a drastic dose of mild mercurous chloride or mass of mercury, U.S.P., followed in eight hours by a saline cathartic. At the end of the twenty-four hour period, scopolamine hydrobromide is given in doses of $\frac{1}{200}$ grain (0.3 mg.) hypodermically at four hour intervals, for three doses. With each dose of scopolamine is given $\frac{1}{40}$ grain (1 mg.) of strychnine sulphate. Following this, the dosage of scopolamine is raised to $\frac{1}{150}$ grain (0.4 mg.) for three doses and then increased to $\frac{1}{100}$ grain (0.6 mg.) accompanied each time with $\frac{1}{40}$ grain strychnine. The total period covered by the administration of scopolamine covers thirty-six hours. When the effects of the scopolamine begin to disappear, if withdrawal symptoms are still quite severe, they are combated with large doses of phenobarbital, or frequently a single dose of $\frac{1}{4}$ grain (16 mg.) of morphine sulphate is given. Treatment from this time on is purely symptomatic, consisting chiefly of sedatives to promote sleep for three or four days as well as small doses of bicarbonate of soda for any gastric distress. Patients are usually discharged at the end of a period of ten days.

## EXPERIMENTAL PROCEDURE

These studies were usually conducted between the first and the fourth day following the disappearance of the mental confusion caused by the scopolamine. Practically all of our observations and studies were made during the morning hours while the subject was reclining in bed, not having had breakfast. The subjects were requested to recline in bed for a period of one-half hour. The figures for the pulse and respiration rates are the averages of a five minute count, and the figures for the blood pressure the average for as many determinations of pressure as could accurately be made in a five minute period. Following these observations, the basal metabolic rate and temperature were measured and recorded. Krogh's apparatus for recording the basal metabolism was used and checked once a week with a subject whose basal metabolic rate was known to be normal. Schneider's test for physical fitness [1] and determinations of vital capacity were usually next in order, followed by the taking of a sample of blood for analysis. The addict was then requested to pass a sample of urine, and following this he was subjected to the climb of two flights of stairs, as described by us in a previous paper.[2] Studies of the reaction to epinephrine and functional tests were carried out, as a rule, with the subjects reclining in bed. The procedure followed in the study of the effect of atropine sulphate on the P-R interval was the same as that described in the paper giving the results obtained during addiction.[2]

## RESULTS

Our results, shown in table 1, indicate that following treatment there was no change in the average pulse rate while the subjects were reclining and the average blood pressures while they were reclining and standing, but there was an average increase of 20 beats per minute in the pulse rate while the subjects were standing and an average increase of 3 respirations per minute while they were reclining. Fifteen of the twenty-three cases after treatment showed a rise in the pulse rate while the subjects were standing as compared to the average rate before treatment; in one, the rate remained the same and in four there was a slight decrease.

Measurements of the heart made by means of the orthodiagram in nine cases before and after treatment showed an average decrease in the ratio of the transverse diameter of the heart to that of the chest of from 44.4 to 41.2 per cent. The average diameter of the aortic arch

1. Schneider, Edward C.: A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency, J. A. M. A. **74**:1507 (May 29) 1920.

2. III: The Circulation and Respiration of Human Addicts During the Administration of Morphine, p. 21.

remained the same, being 4.8 mm. after treatment and 4.7 mm. when morphine was being administered.

Table 2 contains a summary of the average changes obtained in the blood pressure and the pulse and respiration rates following the staircase climbing test both before and after treatment. Charts 1 and 2 show graphically the average absolute readings obtained. The response to staircase climbing following treatment compared with the results obtained during the administration of morphine shows that the immediate increase in the pulse rate was somewhat less than during the administration of the drug. The increase in the respiratory rate and

TABLE 1.—*A Comparison of the Circulation and Respiration of Human Opium Addicts Before and After Treatment with Scopolamine*

| | Before Treatment | After Treatment |
|---|---|---|
| Pulse Rate while Subject Was Reclining: | | |
| Number of cases | 50 | 23 |
| Highest | 84 | 96 |
| Lowest | 52 | 50 |
| Average | 65 | 68.5 |
| Pulse Rate while Subject Was Standing: | | |
| Number of cases | 30 | 23 |
| Highest | 112 | 134 |
| Lowest | 66 | 76 |
| Average | 79 | 99 |
| Blood Pressure while Subject Was Reclining: | | |
| Number of cases | 40 | 24 |
| Highest | 138/92 | 128/84 |
| Lowest | 98/62 | 102/64 |
| Average | 117/72 | 117/74 |
| Blood Pressure while Subject Was Standing: | | |
| Number of cases | 28 | 21 |
| Highest | 138/89 | 118/100 |
| Lowest | 88/64 | 90/ 60 |
| Average | 108/74 | 109/ 75 |
| Respirations: | | |
| Number of cases | 43 | 20 |
| Highest | 22 | 30 |
| Lowest | 10 | 13 |
| Average | 18 | 21 |

failure of the rise in systolic pressure to the height reached during the administration of morphine indicate a slightly poorer response following treatment, if the curves obtained from a series of trained athletes undergoing similar tests are used to show the response of an adequate circulation.

Electrocardiographic studies in a series of eight addicts before and after treatment showed no abnormal changes in the conformation of the various waves. There was a slight decrease in the average P-R interval following treatment, namely, from 0.15 to 0.145 second. At the same time, however, the average rate increased following treatment to 85 beats per minute as compared to 75.8 beats during the administration of morphine. The effect of the injection of $\frac{1}{20}$ grain (3 mg.) of atropine

sulphate was no different after treatment from that while morphine was still being administered. In both studies the P-R interval was decreased 0.02 second, the average decrease coming at approximately the same time, namely, 14.5 minutes before and 12 minutes following treatment. The effect of the atropine on the heart rate was unchanged by treatment. In both instances, the percentage of increase of the heart rate was 45, and the average time of the greatest increase 24.7 minutes during the administration of morphine and 22 minutes following the treatment.

Schneider's test of physical fitness showed a decided fall in the average number of points scored following treatment. Seventeen cases studied during the administration of morphine scored an average of 13.3 points, while the average score following treatment was only 6.9 points. Fifteen of the seventeen cases showed this fall in score, one

TABLE 2.—*A Comparison of the Average Increases of the Pulse, Systolic Pressure and Respiration Rate and Changes in the Diastolic Pressure in Opium Addicts During Administration of Morphine and After Treatment with Scopolamine*

| | | Before Treatment | | | | | | After Treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Number of Cases | 1st Reading | 1st Min. | 2d Min. | 3d Min. | 4th Min. | 5th Min. | 1st Reading | 1st Min. | 2d Min. | 3d Min. | 4th Min. | 5th Min. |
| Pulse | 9 | 62 | 37 | 20 | 13 | 11 | 12 | 57 | 34 | 15 | 6 | 4 | 4 |
| Systolic pressure | 9 | 29 | 30 | 25 | 16 | 9 | 4 | 19 | 23 | 19 | 13 | 7 | 3 |
| Diastolic pressure | 9 | —10 | —7 | —6 | —6 | —6 | —6 | —12 | —7 | —5 | —4 | —1 | —0 |
| Respirations | 9 | .. | 5 | 2 | 1 | 1 | 1 | .. | 9 | 5 | 3 | 2 | 1 |

case scoring the same number of points; the two remaining cases showed a rise of two points following treatment.

Vital capacities in eight cases averaged practically the same while the subjects were receiving morphine as compared to the average obtained following the administration of scopolamine, namely, 4,047 cc. before treatment and 4,016 cc. following treatment.

*The Blood.*—Results obtained from studies of the blood before and after treatment, given in table 3, show practically no significant changes. The average number of red blood cells has increased slightly, namely, 177,000 per cubic millimeter when compared to the results obtained before treatment. The number of white cells has also increased from an average of 9,359 to 11,166. Hemoglobin, differential counts of the white cells and determinations of urea nitrogen, sugar, uric acid, cholesterol, whole blood chloride, serum calcium and serum phosphate all show average results similar to those obtained during addiction. Dry matter of the plasma and of the whole blood has increased slightly, with a slight fall in the dry matter of the cells. The average $p_H$ of the blood has risen from 7.36 to 7.41 following treatment, the carbon dioxide capacity of the

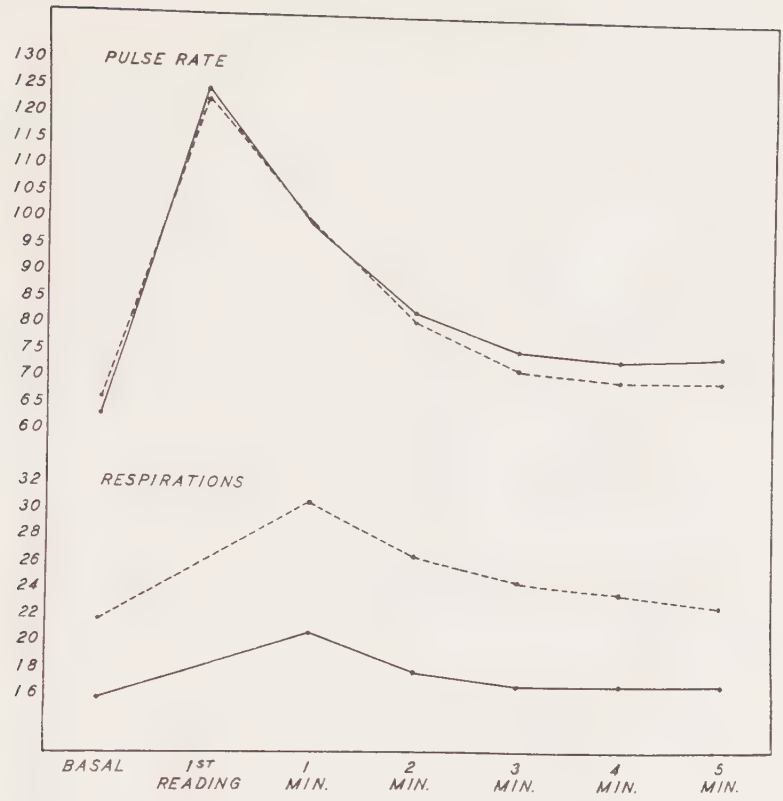



Chart 1.—Average changes in the pulse and respiration rates, in response to staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine. In this chart and in charts 2 and 3, the solid line indicates before treatment and the broken line, after treatment.

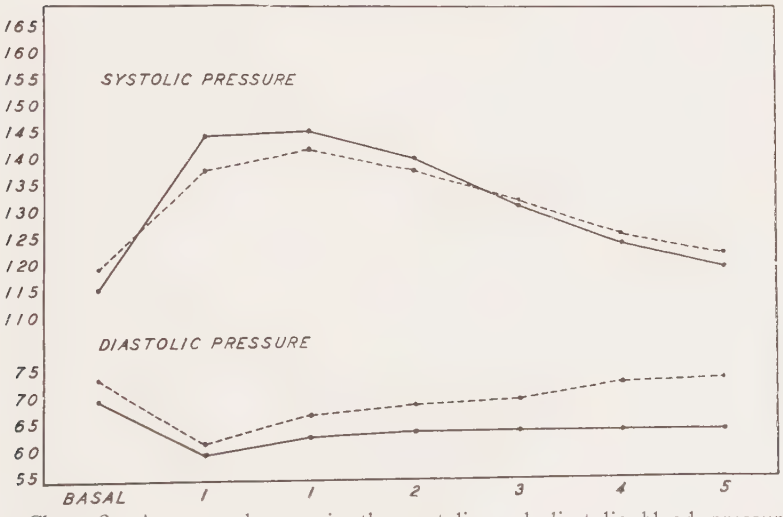



Chart 2.—Average changes in the systolic and diastolic blood pressure in response to the staircase climbing test in a group of human addicts receiving morphine and following treatment with scopolamine.

plasma having fallen from 57.7 to 52 per cent by volume. The average per cent by volume of the red blood cells has increased slightly from 36.2 to 39.4, while the lactic acid of the blood also shows a slight increase following treatment from an average of 25 to 31 mg. per hundred cubic centimeters of blood.

TABLE 3.—*A Comparison of the Physical and Chemical Properties of the Blood of Human Opium Addicts Before and After Treatment with Scopolamine*

| | Hemoglobin, Gm. per 100 Cc. | | Erythrocytes, Number per C Mm. | | Leukocytes, Number per C.Mm. | | Polymorphonuclears, per Cent | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 26 | 19 | 29 | 10 | 33 | 10 | 28 | 7 |
| Highest..... | 19.4 | 18.4 | 4,960 | 5,100 | 15,400 | 16,400 | 78 | 80 |
| Lowest..... | 12.0 | 13.2 | 3,640 | 4,395 | 2,500 | 4,000 | 33 | 45 |
| Average..... | 15.2 | 15.8 | 4,533 | 4,710 | 9,359 | 11,166 | 61 | 61 |

| | Lymphocytes, per Cent | | Large Mononuclears, per Cent | | Eosinophils, per Cent | | Basophils, per Cent | | Blood Urea Nitrogen, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 28 | 7 | 28 | 7 | 28 | 7 | 28 | 7 | 28 | 16 |
| Highest..... | 63 | 53 | 7 | 7 | 2 | 2 | 3 | 2 | 24 | 20 |
| Lowest..... | 20 | 19 | 0 | ½ | 0 | 0 | 0 | 0 | 10 | 9 |
| Average..... | 34 | 35 | 3 | 3 | ½ | ½ | 1½ | ½ | 13.2 | 14 |

| | Blood Sugar, Mg. per 100 Cc. | | Blood Uric Acid, Mg. per 100 Cc. | | Blood Lactic Acid, Mg. per 100 Cc. | | Blood Cholesterol, Mg. per 100 Cc. | | Blood Sodium Chloride, Mg. per 100 Cc. | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 32 | 16 | 22 | 12 | 6 | 6 | 16 | 18 | 9 | 2 |
| Highest..... | 122 | 166 | 4.5 | 4.8 | 31.1 | 38.4 | 280 | 274 | 570 | 560 |
| Lowest..... | 72 | 80 | 2.4 | 2.4 | 20.1 | 22.6 | 158 | 120 | 480 | 490 |
| Average..... | 97 | 100 | 3.3 | 3.4 | 25.0 | 31.8 | 208 | 198 | 511 | 525 |

| | Serum Calcium, Mg. per 100 Cc. | | Serum Phosphate, Mg. of Phosphorus per 100 Cc. | | $p_H$ Plasma | | Carbon Dioxide Capacity of Plasma, per Cent by Volume | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 14 | 5 | 11 | 5 | 20 | 10 | 20 | 10 |
| Highest..... | 14.4 | 13.1 | 3.2 | 2.8 | 7.51 | 7.45 | 71 | 63 |
| Lowest..... | 9.8 | 10.1 | 2.6 | 2.2 | 7.28 | 7.33 | 45 | 48 |
| Average..... | 10.9 | 11.7 | 2.8 | 2.6 | 7.36 | 7.41 | 57.7 | 52 |

| | Dry Matter of Whole Blood, per Cent | | Dry Matter of Plasma, per Cent | | Dry Matter of Cells, per Cent | | Red Blood Cells, per Cent by Volume | |
|---|---|---|---|---|---|---|---|---|
| | Before | After | Before | After | Before | After | Before | After |
| Number of cases.... | 22 | 17 | 15 | 11 | 7 | 8 | 6 | 10 |
| Highest..... | 22.7 | 23.6 | 10.2 | 10.4 | 48.0 | 41.8 | 38.7 | 49.0 |
| Lowest..... | 15.7 | 18.0 | 5.3 | 6.8 | 38.2 | 38.3 | 34.0 | 36.0 |
| Average..... | 20.1 | 21.49 | 8.4 | 9.01 | 41.2 | 40.2 | 36.2 | 39.4 |

Sedimentation tests in twelve cases before and after treatment showed parallel curves indicating no change. Studies of the viscosity of the blood in five cases showed no difference before and after treatment.

*Metabolism.*—The basal metabolic rates of ten addicts obtained during the administration of morphine and again after treatment remained

strikingly constant. The average range before treatment was between —9 and +9 and following treatment between —14 and +9. Individual determinations showed the lowest and highest rates before treatment to be —26 and +28 and following treatment —28 and +26.

*Changes in Weight.*—The loss of weight during treatment in some cases was striking. Twenty patients whose weights were taken just before and after treatment showed an average loss of 7 pounds (3.2 Kg.). The greatest loss was 18 pounds (8.2 Kg.), while one patient actually gained 3 pounds (1.4 Kg.). The other eighteen cases showed losses of weight of from 2 to 12 pounds (0.9 to 5.4 Kg.), respectively.

*Temperature.*—Temperatures taken in a series of 100 addicts during treatment and for a period of three days following the cessation of the administration of scopolamine showed a slight rise for forty-eight hours in seventy-eight of the cases. The highest temperature recorded was 100.8 F., the average maximum temperature in the seventy-eight cases being 99.4. These patients were all free from abscesses and intercurrent infections. This slight rise in temperature rarely continued for more than forty-eight hours, although one addict had an average temperature of 99.2 for a period of five days, which rose at times to as high as 100.

*The Kidneys.*—The urines of 100 addicts showed a definite rise in the average specific gravity of from 1.018 to 1.026, with a distinctly lower twenty-four hour output following treatment. In two cases, a trace of sugar was found with Benedict's test following treatment. Thirty-two cases showed the presence of from a trace to a light cloud of albumin, ten cases showing a few granular and hyaline casts. Spermatozoa were frequently found in the urine following treatment.

Phenolsulphonphthalein tests in eight cases studied before and after treatment showed an average two hour elimination of 64 per cent of the dye before treatment and of 48 per cent after treatment. Five of these eight cases showed albumin in the urine following treatment, one case showing a light cloud. The latter patient eliminated 49 per cent of the dye before treatment and only 16 per cent following treatment during the two hour periods. The other seven cases showed slight decreases in the amounts excreted after treatment compared to the results obtained during the administration of morphine.

*The Liver.*—The phenoltetrachlorphthalein test carried out in four cases showed no delay in the disappearance of the dye in two hours either before or after treatment. Van den Bergh's tests remained negative in four cases both before and after treatment. An average icterus index of 6.1 was obtained following treatment as compared to an average of 5.5 obtained before treatment.

*Blood Sugar Response to Epinephrine.*—Chart 3 shows graphically the blood sugar response in a series of five addicts who were given 1 cc. of 1:1,000 epinephrine hydrochloride both before and after treatment. The curves show that the blood sugar content rises slightly higher following treatment as compared to the rise while morphine is being administered. Determinations of blood pressure were also made, but the results were so variable as to make any comparison doubtful in value.

## COMMENT AND LITERATURE

The interpretation of our results in the light of the behavior and appearance of the addicts following treatment is extremely difficult.

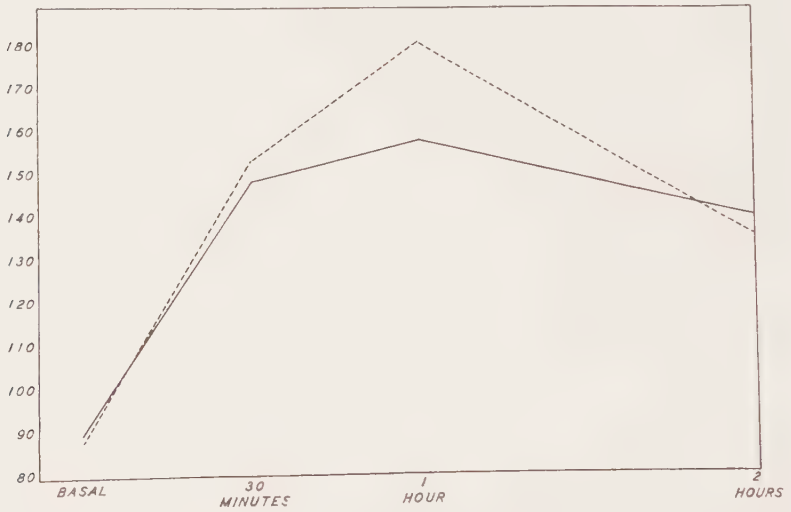



Chart 3.—Average blood sugar response to the injection of 1 cc. of epinephrine hydrochloride (1:1,000) in a group of human addicts receiving morphine, and after treatment with scopolamine.

The effect of the drastic purgation and the scopolamine itself must be considered in the production of the changes observed, but in general our observations following treatment are more or less similar to those obtained during a series of studies made following a forty-eight hour period of abrupt withdrawal without the substitution of any other drug.[3]

Lambert and Tilney [4] studied the blood of a series of opium addicts before and during treatment with narcosan. They did not find any

3. VI: The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, p. 51.

4. Lambert, Alexander, and Tilney, Frederick: Treatment of Narcotic Addiction by Narcosan, M. J. & Rec. **124**:764 (Dec. 15) 1926.

changes in the uric acid and creatinine of the blood either before or during treatment. Wide fluctuations of the blood sugar, which we interpret as being standard, are reported one hour after breakfast was taken. Our blood sugar values remained constant in specimens taken before and after treatment while the addict was fasting. Lambert and Tilney [4] also found considerable fluctuation of the carbon dioxide chemically bound in the plasma and detected an increase in acidosis for the first three days of treatment. In the majority of our cases, the average $p_H$ of the blood shows a tendency for a slight increase in the alkalinity following treatment. Our blood cell determinations are similar to those obtained by Lambert and Tilney except that we encountered certain slight degrees of leukocytosis before treatment was begun. Our urinary observations are also identical with those of Lambert and Tilney.[4]

In a comparative study of the efficiency of the narcosan treatment with the routine treatment employed in the Colorado Psychopathic Hospital, Johnson [5] was unable to detect any significant changes in the blood. He found but one abnormal blood sugar value, while his figures for blood urea nitrogen were well within normal limits. Johnson found a leukocytosis in most cases during narcosan treatment, the actual figures obtained ranging between 5,400 and 19,300 cells.

Immediately following treatment, the appearance and behavior of the addicts are misleading. It has been our frequent experience to have two addicts in the ward whose needs were supplied with the same amount of morphine and who were given identical treatment at the same time. At the end of the fourth day, one addict will be up and about the ward with the declaration that he feels fine and will eat well and boastfully proclaim that he is through with the drug. The other addict will remain in bed, refuse food, appear miserable and complain bitterly of extreme weakness and nervousness. We believe that frequently neither of these two types is expressing or acting his real self. The addict who proclaims his well-being may or may not show the few positive changes we have previously noted. We are convinced that a good deal of this behavior is feigned, and that the addict is trying to gain his discharge in order that he may return to his friends who will again supply him with drugs.

The other addict who complains of being so miserable and weak and nervous may or may not show any of the positive symptoms previously mentioned. This behavior is frequently found in addicts who are penniless and who do not know where to turn for drugs when discharged from the ward.

5. Johnson, George S.: The Use of Narcosan in the Treatment of Drug Addiction, Colorado Med. **24**:347 (Nov.) 1927.

It is during this period of the addict's stay in the ward that our method of treatment is characterized as being the best or the worst that the addict has ever undergone.

Few of our addicts have not had treatments before. Many of them have tried every method employed for the treatment of narcotic addiction. Their comments as to the efficacy of these various forms of treatment are totally unreliable. It is our opinion, however, from the number of addicts who have come to us from other institutions and the fact that 50 per cent come back to us for another treatment, that present methods, including our own, leave much to be desired.

## CONCLUSIONS

Studies of a series of opium addicts before and after treatment with scopolamine revealed the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the $p_H$ of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenoltetrachlorphthalein test of liver function, icterus index, van den Bergh's tests, and response of the blood sugar to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive symptoms and yet appear and behave as though he were normal. On the other hand, he may give the appearance of one who is quite ill and yet not show any of the foregoing positive symptoms.

## VIII. THE EFFECTS OF INTRAMUSCULAR AND INTRAVENOUS ADMINISTRATION OF LARGE DOSES OF MORPHINE TO HUMAN ADDICTS

Wide variations in the quantity of the drug used and also in the frequency of administration to prevent withdrawal symptoms are encountered among different human addicts as well as in the same addict at various periods during addiction. This variation is found not only in dosage and frequency of administration, but also in the methods of administration. The choice as to the latter in 95 per cent of our cases was the hyperdermic method, but sniffing of heroin, oral administration, pipe smoking of opium and intravenous administration were also encountered. With these variations in mind we administered additional amounts, both intramuscularly and intravenously, in order to determine, first, what physiologic effects are brought about in human addicts by quantities greater than those required to prevent withdrawal symptoms; second, whether abrupt withdrawal for a period of forty-eight hours decreases the intravenous tolerance of the addict, and third whether these additional amounts prolong the period of comfort on the part of the addict.

Samples of blood were analyzed for morphine by Dr. A. K. Balls [1] of the Department of Pharmacology, University of Pennsylvania, immediately following the completion of the injection.

### EXPERIMENTAL PROCEDURE

Five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four used the hypodermic method, volunteered as subjects for the experiments planned. All of the experiments, whether the drug was given intramuscularly or intravenously, were made while the patients were reclining in bed for at least half an hour without having had breakfast. Except in the cases in which morphine was withheld for a period of forty-eight hours, the regular dosage was given intramuscularly, usually about 8:30 a. m.

The morphine sulphate solution used in these experiments was especially prepared by the department of pharmacology of the University of Pennsylvania in an isotonic solution of sodium chloride, 5 cc. containing 2 grains (0.13 Gm.) of morphine sulphate. When the drug was given intramuscularly, the point of injection was usually over the anterior part of the chest or in such areas as appeared to be free from recent injections. The intravenous administration was always given into the

1. Balls, A. K., and Wolff, W. A.: The Determination of Morphine, J. Biol. Chem. **80**:379 (Dec.) 1928.

median basilic vein. In all cases of intravenous administration, 2 grains was given at each injection, except in one case following a period of withdrawal for forty-eight hours, when at the close of the experiment the dosage for several injections was raised to 4 grains (0.26 Gm.).

The observer who administered the drug reported the general behavior and color of the skin of the subject, as well as any remarks on his part. Another observer confined his attention to the blood pressure, a third to the counting of the pulse and a fourth to the respirations. The figures for blood pressure are the average for as many as could be accurately taken in a five minute period. The figures for pulse rate and respirations are the averages of a five minute count. In the protocols of two experiments given in this paper are found the actual figures and the remarks made by the addict during the entire period of administration. Samples of blood for the analyses reported were taken just before the administration of the drug was begun and, as a rule, about fifteen or twenty minutes following the last dosage. In four cases, electrocardiographic studies were made preceding the administration and immediately following the last dosage given.

The actual time required for each injection of 2 grains varied from one minute and twenty seconds to four minutes and twenty-two seconds, depending on the reaction of the patient.

## RESULTS

Tables 1, 2 and 3 contain the data obtained from the various experiments. Chart 1 shows graphically the changes in blood pressure, respiration and pulse rate obtained in an experiment in which 30 grains (1.95 Gm.) of morphine sulphate was given intravenously to an addict over a period of two hours and twenty-four minutes, he having previously received his normal dosage of 17 grains (1.1 Gm.) in twenty-four hours. Protocols 1 and 2 give the actual determinations of blood pressure, pulse and respiratory rates during the intravenous administration of morphine sulphate to the same addict during his regular dosage and following a forty-eight hour period of withdrawal. The protocols also contain the remarks of the patient as well as such observations as were deemed important.

In the three cases in which the morphine was administered intramuscularly in dosages of six, four and three times the amount to which the addicts were accustomed, no significant changes in the pulse, respiration, blood pressure, P-R interval, blood reaction or blood content in dry matter, urea nitrogen or sugar could be found. In one case the blood pressure fell from 116 systolic, 68 diastolic to 106 systolic, 64 diastolic, but in another it rose from 90 systolic, 68 diastolic to 102 systolic, 64 diastolic; in the third, the change was within the error of reading.

TABLE 1.—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intramuscularly to Human Opium Addicts*

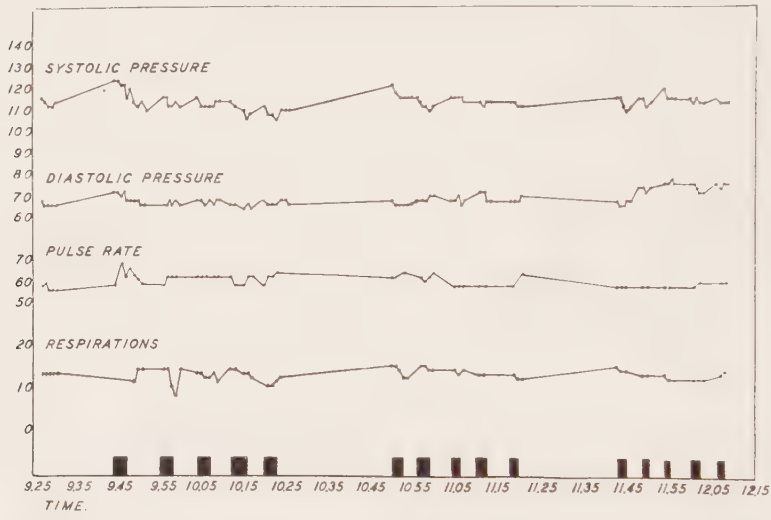
| Time and Case No. | Dosage of Drug, Grains | Blood Pressure | Respirations per Minute | Pulse per Minute | P-R Interval, Seconds | $p_H$ of Blood | Sugar, Mg. per 100 Cc. | Urea Nitrogen, Mg. per 100 Cc. | Dry Matter of Whole Blood |
|---|---|---|---|---|---|---|---|---|---|
| Case 26-35 | | | | | | | | | |
| 9:55 a. m. | .. | 104/61 | 10 | 55 | 0.155 | 7.33 | 90 | 11 | 20.40 |
| 9:57 a. m. | 5 | 104/61 | | | | | | | |
| 11:11 a. m. | 6 | | | | | | | | |
| 11:53 a. m. | 6 | | | | | | | | |
| Total | 17 | | | | | | | | |
| 12:00 noon | | 101/55 | 9 | 60 | 0.160 | 7.32 | 92 | 10 | 19.16 |
| Case 26-85 | | | | | | | | | |
| 9:50 a. m. | .. | 90/68 | 8 | 66 | 0.156 | 7.40 | 80 | 12 | 20.23 |
| 9:56 a. m. | 3 | | | | | | | | |
| 10:56 a. m. | .. | 98/60 | 8 | 60 | | | | | |
| 11:14 a. m. | 4 | | | | | | | | |
| 11:52 a. m. | 4 | | | | | | | | |
| Total | 11 | | | | | | | | |
| 12:29 p. m. | | 102, 64 | 10 | 58 | 0.172 | 7.38 | 90 | .9 | 19.69 |
| Case 26-39 | | | | | | | | | |
| 10:34 a. m. | .. | 116/68 | 14 | 60 | | | | | |
| 10:35 a. m. | 5 | | | | | | | | |
| 11:07 a. m. | .. | 108/62 | 13 | 59 | | | | | |
| 11:10 a. m. | 5 | | | | | | | | |
| Total | 10 | | | | | | | | |
| 11:31 a. m. | | 106/64 | 14 | 60 | | | | | |

TABLE 2.—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intravenously to Human Opium Addicts*

| Case No. | Pulse | Respirations | Blood Pressure | P-R Interval, Seconds | Hemoglobin | Dry Matter of Whole Blood | Oxygen Content of Venous Blood | Percentage Saturation of Oxygen of Venous Blood | $p_H$ of Blood |
|---|---|---|---|---|---|---|---|---|---|
| 26-21 | | | | | | | | | |
| Before injection | 85 | 22 | 126/68 | 0.176 | 14.9 | 20.83 | 9.3 | 62.4 | 7.45 |
| After injection 14 grains, 2 hours* | 68 | 18 | 118/76 | 0.184 | 14.4 | 20.27 | 11.3 | 78.5 | 7.41 |
| 26-39 | | | | | | | | | |
| Before injection | 60 | 14 | 115/68 | 0.160 | | | | | |
| After injection 30 grains, 2 hours 23 minutes* | 62 | 14 | 116/68 | 0.160 | | | | | |
| 26-56 | | | | Erythrocytes | Leukocytes | | | | |
| Before injection | 72 | 12 | 117/69 | 4,560,000 | 6,600 | | | | |
| After injection 6 grains, 1 hour 37 minutes | 73 | 11 | 122/70 | 4,640,000 | 5,800 | | | | |

* Analysis of the blood for the presence of morphine sulphate by Dr. Balls (J. Biol. Chem. **80**: 379 [Dec.] 1928) of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg. per 25 cc. of blood, equivalent to approximately 4 grains in total blood.

When the drug was administered intravenously to three different patients in dosages of seven, nine and six times the usual quantity, there was no change in the pulse rate, respiration and blood pressure in two. Hemoglobin, the dry matter of the whole blood and the blood reaction showed no significant change in the one case in which analysis of the blood was made. In one addict given nine times the usual dose, the P-R interval remained the same, but in the subject given seven times the usual dosage it was prolonged from 0.176 to 0.184 second. In the latter case, however, the pulse rate dropped from 85 to 68 per minute, the blood pressure fell from 126 systolic, 68 diastolic to 118 systolic, 76 diastolic, and the respirations from 22 to 18 per minute. This patient (case 26-21) showed definite signs of fear before the injections were




Effect on pulse rate, blood pressure and respiration of 30 grains (1.95 Gm.) of morphine sulphate given intravenously to a human addict over a period of two hours and twenty-four minutes. The shaded areas indicate the time of injections, of 2 grains each.

begun. As the injections proceeded and no untoward results were felt, whether because of the action of the drug or not, this addict showed less apprehension, which we believe to be the factor in these changes. The percentage of oxygen saturation of the venous blood taken from the same vein at the elbow rose from 62.4 to 78.5. A count of the red and white blood cells made in one case showed no change.

The two cases studied during the intravenous injection of morphine sulphate following a withdrawal period of forty-eight hours both showed rises in the pulse rate and a slight fall in the pressure. Respirations decreased slightly in one and remained the same in the other. There was a rise in the number of red blood cells of 400,000 per cubic

millimeter in the one case and of 180,000 in the other. The white blood cell count per cubic millimeter of blood fell slightly in one and rose correspondingly in the other.

The differential counts, Arneth counts and the fragility of the cells as well as the coagulation time remained practically the same. In one case, the dry matter of the whole blood rose slightly as did the hemoglobin, but the dry matter of the plasma remained the same. The blood $p_H$ fell from 7.44 to 7.39; the carbon dioxide capacity remained the same.

TABLE 3.—*The Effects of the Administration of Morphine Sulphate Intravenously Following a Forty-Eight Hour Withdrawal Period in Human Opium Addicts*

| | Case 26–21 | | Case 26–39 | |
|---|---|---|---|---|
| | At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate | Following Administration of the Morphine Sulphate, 11 Grains, in 1 Hour 16 Minutes | At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate | Following Administration of the Morphine Sulphate, 20 Grains, in 53 Minutes* |
| Pulse | 80 | 96 | 72 | 79 |
| Respirations | 21 | 18 | 11 | 11 |
| Blood pressure | 132/74 | 122/70 | 109/64 | 102/63 |
| Erythrocytes | 5,150,000 | 5,550,000 | 5,240,000 | 5,420,000 |
| Leukocytes | 10,800 | 12,200 | 13,300 | 12,700 |
| Differential count: | | | | |
| Polymorphonuclears | 77 | 79 | 76 | 73 |
| Lymphocytes | 20 | 19 | 21 | 25 |
| Transitionals | 2 | 1 | 3 | 2 |
| Basophils | 1 | 0 | | |
| Large mononuclears | 0 | 1 | | |
| Baskets | 4 | 5 | | |
| Arneth: | | | | |
| Old | 68 | 61 | 68 | 67 |
| New | 32 | 39 | 32 | 33 |
| Fragility: | | | | |
| Complete | 36 | 36 | 32 | 30 |
| Partial | 44 | 44 | 48 | 48 |
| Coagulation | 2 min. | 1 min. 50 sec. | 2 min. | 1 min. 40 sec. |
| $p_H$ | 7.44 | 7.39 | | |
| Carbon dioxide capacity | 54 | 56 | | |
| Hemoglobin | 16.1 | 16.9 | | |
| Percentage of saturation of oxygen of venous blood | 61.7 | 84.1 | | |
| Dry matter of whole blood | 22.22 | 22.59 | | |
| Dry matter of plasma | 9.59 | 9.64 | | |

* Analysis of the blood for the presence of morphine sulphate by Dr. Balls of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg. per 25 cc. of blood.

There was a rise of from 61.7 to 84.1 in the percentage of oxygen saturation of venous blood drawn from the vein.

The behavior of the addicts following the large doses given both intravenously and intramuscularly is of considerable interest. In the three cases studied following intramuscular injection, it was impossible to detect any change in appearance. One addict stated that he felt "loaded"; the other two expressed their feelings as being unchanged during the injections. There was no evidence of drowsiness. Interest was shown in the surroundings, and an occasional cigaret was smoked. One subject read the newspaper when observations were not being taken.

All three requested their usual dosage at the next regular interval and ate their regular meals.

Two of the three addicts who acted as the subjects for intravenous injections of morphine during regular administration served also as the subjects for the intravenous administration following a forty-eight hour withdrawal period. The patient in case 26-39 had occasionally used the intravenous method of administration during addiction outside the ward but while in the ward was given the drug hypodermically.

During the intravenous administration of the drug during the period of regular dosages, the patients in cases 26-21 and 26-56 complained at times of itching and severe tingling in the extremities, back of the neck and face, as well as over the anterior part of the chest, which would last for a minute or two while the drug actually was being injected. At one time during the injection, the addict in case 26-21 complained bitterly of a pain in his head as if he "were hit in the head with a baseball bat" and again, as he expressed it, "as if someone were jabbing his knuckles in the back of my head." Yet a few minutes later he would state that he felt fine and was as well as if he had never taken drugs in his life. At the time that the patients stated that they experienced these sensations, no changes could be noticed by the observers in the pulse rate, respiration and blood pressure, although there appeared to be an increased redness of the face, neck and anterior part of the chest. On the other hand, the addict in case 26-39 who received by far the largest doses during the intravenous administration scarcely felt any of the sensations described by the other two. It is true that he had at times been accustomed to intravenous administration, and he said that he was familiar with these sensations but that he felt them only slightly and not enough to annoy him.

Protocol 2 gives in detail the observations and remarks of patient 26-39 during the intravenous administration following the forty-eight hour withdrawal period. They need no comment, except again to call attention to the fact that during the last dose of 4 grains the subject requested a hpodermic injection into the muscle. The experiment was finished at 11:05 a. m., at which time he was given 3 grains hypodermically. At 3 p. m., he requested another hypodermic injection of 3 grains. Between these two intervals, he was about the ward as usual, read a newspaper and ate a hearty lunch.

The reaction of patient 26-21 who received 11 grains intravenously in one hour and sixteen minutes following a forty-eight hour withdrawal period was similar to that in patient 26-39. He was considerably more nervous than patient 26-39. The violent twitching of the labial muscles present before the injections were begun became considerably less evident only after the seventh grain was injected, at an interval of one hour and six minutes after the injection of the first two grains. These

twitchings were still slightly present after the last dosage of a total of 11 grains. This patient complained at times of feeling on fire and of "that awful tingling in the body." However, careful observations of blood pressure and pulse and respiration rates again showed no marked changes during these complaints. His face and neck and the anterior part of the upper half of the chest also showed the brilliant red color found in case 26-39, and he scratched this area at frequent intervals. At the end of the experiment he complained of feeling drowsy, but he immediately got up from the bed, started conversing with several other addicts and ate his regular lunch. He slept for a short interval following his lunch, but at 4 p. m. requested his usual dosage of 2 grains of morphine hypodermically.

PROTOCOLS

PROTOCOL 1 (case 26-39).—*The Intravenous Administration of 30 Grains (1.9 Gm.) of Morphine Sulphate in Two Hours and Twenty-Four Minutes.*

This subject, aged 29, had been addicted to the use of the drug for 13 years (?). He was 5 feet 10½ inches (179 cm.) tall and weighed 220 pounds (99.7 Kg.) He had received a dosage of morphine sulphate of from 21 to 25 grains (1.36 to 1.62 Gm.) per twenty-four hours in the ward for the last five days. On the day of the experiment, Feb. 14, 1927, the patient did not receive breakfast.

8:30 a. m.: Morphine sulphate, 4 grains (0.26 Gm.) given hypodermically.
8:45 a. m.: Patient reclining in bed.

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 9:26 a. m. | | | | |
| 9:27.15 seconds | 118/70 | 14 | 60 | |
| 9:27.55 seconds | 116/68 | 14 | 61 | No comment on part of patient. |
| 9:28.37 seconds | 114/68 | 14 | 58 | |
| 9:29.25 seconds | 114/68 | 14 | 58 | |
| 9:30.10 seconds | 116/68 | 14 | 58 | |
| 9:44 a. m. Intravenous injection of 2 grains (0.13 Gm.) morphine sulphate begun. | | | | |
| 9:44.22 seconds | 126/74 | | 60 | |
| 9:45.08 seconds | 126/74 | | | |
| 9:45.10 seconds | | | | Felt a little tingling sensation. "I have not got the kick yet." |
| 9:45.46 seconds | 124/72 | | 70 | |
| 9:46.25 seconds | 124/74 | | | |
| 9:46.36 seconds | | | | Did not feel anything. |
| 9:47.01 seconds | 118/70 | | 64 | |
| 9:47.49 seconds | 122/70 | | 68 | |
| | Injection finished. | | | |
| 9:49.07 seconds | 116/70 | 12 | 65 | |
| 9:50.12 seconds | 114/70 | 15 | 63 | |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 9:51.07 seconds | 116/68 | 15 | 61 | |
| 9:51.49 seconds | 112/68 | | | Patient did not feel the slightest thing. "No kick at all." |
| 9:55 a. m.: Second dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 9:56.09 seconds | 118/68 | 15 | 60 | |
| 9:56.46 seconds | 118/68 | | | |
| 9:57.29 seconds | 114/70 | 15 | 64 | |
| 9:58.24 seconds | 114/68 | 11 | 64 | |
| | Injection finished. | | | Patient dozed. |
| 9:59.26 seconds | 116/70 | 9 | 64 | "How do you feel?" "Just flushing up a little, that's all." |
| 10:00.37 seconds | 114/68 | 15 | | |
| 10:04 a. m.: Third dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:04.49 seconds | 118/70 | 14 | 64 | |
| 10:05.34 seconds | 114/70 | 14 | 64 | |
| 10:06.25 seconds | 114/68 | 13 | 64 | |
| 10:07.16 seconds | 114/70 | 13 | | |
| | Injection finished. | | | |
| 10:08.11 seconds | 114/68 | 14 | 64 | Patient denied any feeling of tingling or flushing up. "I do not feel any different, just the same." |
| 10:08.54 seconds | 116/70 | | | |
| 10:09.47 seconds | 116/70 | 12 | 64 | |
| 10:12 a. m.: Fourth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:12.56 seconds | 116/68 | 15 | 64 | |
| 10:13.58 seconds | 114/68 | 15 | 60 | |
| 10:15.02 seconds | 112/66 | 14 | 60 | |
| 10:15.54 seconds | 108/68 | 14 | 64 | |
| | Injection finished. | | | Patient still said, "I feel all right." |
| 10:16.55 seconds | 110/66 | 13 | 64 | |
| 10:20 a. m.: Fifth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| before start | 114/70 | 11 | 60 | |
| 10:21.26 seconds | 110/68 | 11 | 64 | |
| 10:22.15 seconds | 110/68 | 12 | 64 | |
| 10:23.24 seconds | 108/68 | 13 | 66 | |
| | Injection finished. | | | |
| 10:24.06 seconds | 112/70 | | | |
| 10:25.00 seconds | 112/70 | | | Patient felt drowsy; dozed just sitting up in chair smoking. Said he was not hungry. |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 10:25.48 seconds | 112/68 | | | |
| 10:30 a. m.: Blood drawn. | | | | |
| 10:50 a. m.: Sixth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:50.39 seconds | 124/70 | 16 | 64 | |
| 10:51.30 seconds | 120/68 | 16 | 64 | |
| 10:52.15 seconds | 118/68 | 15 | | |
| 10:53.01 seconds | 118/68 | | | |
| | Injection finished. | | | Patient still denied any sensations. "I feel all right." |
| 10:53.42 seconds | 118/68 | 13 | 66 | |
| 10:54.30 seconds | 118/68 | 13 | | |
| 10:56 a. m.: Seventh dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:56.04 seconds | 118/70 | | | |
| 10:56.44 seconds | 116/68 | | | |
| 10:57.31 seconds | 114/70 | 16 | 64 | |
| 10:58.16 seconds | 114/70 | 16 | 62 | |
| 10:59.02 seconds | 112/72 | 15 | 64 | "I feel all right. No, I have not felt any tingling." |
| | Injection finished. | | | |
| 10:59.53 seconds | 114/72 | 15 | 66 | |
| 11:04 a. m.: Eighth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| before start | 118/70 | | | |
| 11:04.40 seconds | 118/70 | | | |
| 11:05.40 seconds | 118/72 | 15 | 60 | |
| 11:06.23 seconds | 118/68 | 14 | 60 | |
| 11:07.03 seconds | Injections finished. | | | |
| 11:07.08 seconds | 116/70 | 15 | 60 | "I feel all right." |
| 11:10 a. m.: Ninth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 11:10.41 seconds | 116/74 | | | |
| 11:11.16 seconds | 112/74 | 14 | 60 | |
| 11:12.01 seconds | 116/70 | | | "That's the time I felt it." Itching around face and at back of neck. |
| 11:12.58 seconds | 116/70 | 14 | 60 | |
| 11:13.59 seconds | Injection finished. | | | |

Patient lay on the bed most of the time with his eyes closed. Looked peaceful enough. Was not much interested in the actions going on around him. "What am I thinking about?" "Oh, nothing, just resting. Just thinking of things in general, nothing in particular. I am perfectly satisfied. I am thinking of what I am going to eat." "Oh, no, I do not think I could stay this way the rest of my life."

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 11:18 a. m.: Tenth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 11:18.52 seconds | 116/70 | | | |
| 11:19.35 seconds | 116/70 | 14 | 60 | |
| 11:20.15 seconds | 114/70 | 13 | | |
| 11:20.54 seconds | Injection finished. | | | |
| 11:21.04 seconds | 114/72 | 13 | 66 | |
| 11:22 a. m.: Blood drawn. | | | | |
| 11:43 a. m.: Eleventh dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 11:43.22 seconds | 118/70 | | | |
| 11:43.56 seconds | 118/68 | 16 | 60 | |
| 11:44.40 seconds | 114/68 | 15 | 60 | |
| 11:45.25 seconds | 112/70 | 15 | 60 | Patient said he felt the "pins and needles" slightly that time. |
| 11:46.04 seconds | Injection finished. | | | |
| 11:46.10 seconds | 114/70 | | | |
| 11:48 a. m.: Twelfth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 11:48.12 seconds | 118/76 | 14 | 60 | |
| 11:49.01 seconds | 118/76 | 14 | 60 | |
| 11:49.57 seconds | 114/74 | | | |
| | Injection finished. | | | |
| 11:50.30 seconds | 116/76 | | | |
| 11:54 a. m.: Thirteenth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| before start | 122/78 | | | |
| 11:54.52 seconds | 118/78 | 14 | 60 | |
| 11:55.42 seconds | 118/80 | 13 | 60 | |
| 11:56.00 second | Injection finished. | | | "Outside of that little tingling sensation, I don't feel anything." |
| 11:56.20 seconds | 118/78 | | | |
| 12:00 noon: Fourteenth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| before start | 118/78 | | | |
| 12:00.46 seconds | 116/78 | | | |
| 12:01.35 seconds | 118/76 | 13 | 60 | |
| 12:02.22 seconds | 116/74 | 13 | 62 | |
| 12:02.48 seconds | Injection finished. | | | |
| 12:03.04 seconds | 116/74 | 13 | | |
| 12:06 p. m.: Fifteenth dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| 12:06.42 seconds | 118/78 | | | |
| 12:07.20 seconds | 116/76 | 14 | 62 | |
| 12:07.52 seconds | 116/78 | | | |
| 12:08.24 seconds | Injection finished. | | | |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 12:08.29 seconds | 116/78 | 15 | 62 | |
| 12:45 p. m.: Blood drawn. | | | | |
| 12:47 p. m.: Electrocardiogram. | | | | |
| Twice during the experiment, the patient asked for and received a glass of water. | | | | |

PROTOCOL 2 (case 26-39).—*The Intravenous Administration of 20 Grains (1.3 Gm.) of Morphine Sulphate in a Period of Fifty-Six Minutes Following a Withdrawal Period of Forty-Eight Hours.*

This subject, aged 29, had been addicted to the use of the drug for years (?) He was 5 feet 10½ inches tall and weighed 216 pounds (98 Kg.). The daily dosage in the ward for the last twenty-three days has been from 21 to 25 grains of morphine sulphate per twenty-four hours; eighteen days previous to this experiment he received 30 grains of morphine sulphate intravenously in a period of two hours and fifty-three minutes. For the past forty-eight hours, the drug had been withheld.

At 9.27 a. m., the patient was reclining in bed. The visible signs of withdrawal were frequent yawning, lacrimation, dilated pupils, slight cough, difficulty in breathing through the nose, occasional tremor of the right leg and extreme nervousness manifesting itself mostly in begging for the experiment to begin. The subject appeared to be suffering with a severe cold. No rise in temperature occurred.

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 9:32.25 seconds | 110/64 | 11 | 75 | Yawned. |
| 9:33.01 seconds | 110/66 | 12 | 74 | |
| 9:33.36 seconds | 108/62 | 12 | 74 | Yawned. |
| 9:34.08 seconds | 110/64 | 12 | 70 | |
| 9:34.47 seconds | 110/64 | | | |
| 9.36 a. m. | | | 72 | Coughed. |
| 9:38 a. m. | | | | |
| 9:38.40 seconds | 110/64 | | | |
| 9:39.18 seconds | 110/66 | 16 | 71 | |
| 9:40.05 seconds | 110/64 | | | Coughed. |
| 9:40.35 seconds | 110/64 | 16 | 75 | |
| 9:41.10 seconds | 112/64 | | | Yawned. |
| 9:41.18 seconds | | 14 | 76 | Coughed. |
| 9:41.54 seconds | 114/66 | | | |
| 9:42.35 seconds | 112/64 | 16 | 73 | |
| 9:42.40 seconds | | | | Coughed. |
| 9:43.23 seconds | 112/68 | 14 | 72 | Yawned, moving feet. |
| 9:44.05 seconds | 112/68 | | | Yawned, moving feet. |
| 9:44 a. m.: Coughed and yawned. | | | | |
| 9:45 a. m.: Testing of reflexes of knees. | | | | |
| 9:49 a. m.: Blood drawn. | | | | |
| 9:52 a. m.: Yawned. | | | | |
| 9:58 a. m.: Patient rose up in bed in anticipation. | | | | |
| 10:00 a. m.: Yawned and said: "Give me the shot and a damp towel for the back of my neck, that's all." Yawned twice more. | | | | |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 10:02 a. m.: How do you feel?" "I am aching all over and yawning. I feel sick at my stomach. There's nothing quiet about me. My nose feels stopped up. I could vomit. Gagging, that's what that cough is, but the minute you shoot it in the vein I will feel better." | | | | |
| 10:05 a. m.: First dosage of 2 grains of morphine sulphate, intraveneously, begun. | | | | |
| 10:05.12 seconds | 116/68 | | | |
| 10:06.05 seconds | 114/66 | 24 | 70 | |
| 10:06.12 seconds | | | | "I feel it now—my nose is cleared up. No other sensation. My nose has stopped running. It dries right up." |
| 10:07.01 seconds | 116/64 | 12 | 72 | No other sensations. No tingling or pain in back of neck. "You are going too slow." |
| 10:07.13 seconds | Injection finished. | | | |
| 10:07.45 seconds | 110/66 | 12 | | |
| | | 11 | | |
| 10:11 a. m.: Second dosage of 2 grains of morphine sulphate, intravenously, begun. | | | | |
| before start | 112/68 | | | |
| 10:11.15 seconds | 114/66 | | | |
| 10:11.57 seconds | 116/68 | | | |
| 10:12.12 seconds | | 12 | 72 | "I can feel it now. Through the shoulders. Sort of pulls together. Your nerves get quiet. I feel warmer now." |
| 10:12.28 seconds | | | | "My cold has gone now. Eyes are not watering, but you do not get relieved, not yet. Twitches have not gone yet. Only in that right leg." |
| 10:12.56 seconds | 112/70 | 11 | 72 | |
| | Injection finished. | | | |
| 10:13.35 seconds | 112/76 | 11 | 72 | |
| 10:16 a. m.: Third dosage of 4 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:16.25 seconds | 108/68 | | | |
| 10:16.55 seconds | 112/70 | 20 | 80 | "My knees are beginning to relax." |
| 10:17.23 seconds | | 12 (½ min.) | | |
| 10:17.30 seconds | 112/68 | | 80 | |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 10 : 18.20 seconds | 112/68 | | | "Twitching of legs and knees. I have that twitchy feeling in just that right leg." |
| 10 : 19.14 seconds | | | | "Now I am just getting that 'weight' in my stomach." |
| 10 : 19.20 seconds | 108/70 | | | "I am beginning to flush up. You don't get that pins and needles when you go so slow." |
| 10 : 19.26 seconds | | | 80 | |
| 10 : 20.26 seconds | 110/68 | | | |
| 10 : 20.55 seconds | | | | "Now I got that tinge that sort of makes your face and hands swell up." |
| | Injection finished. | | | |
| 10 : 21.20 seconds | 108/68 | | | Patient's ears were extremely red but he said that they did not burn. |
| 10 : 24 a. m. : Fourth dosage of 4 grains of morphine sulphate, intravenously, begun. | | | | |
| 10 : 24.30 seconds | 112/68 | | | |
| 10 : 25.25 seconds | | 13 | 62 | Patient denied feeling |
| 10 : 25.30 seconds | | | | drowsy. "I feel better than I did, yes." |
| 10 : 25.34 seconds | 108/68 | | | "Could I stand more? Sure, your nerves seem to eat it right up as soon as you get it." |
| 10 : 26.15 seconds | 110/68 | 12 | 84 | |
| 10 : 27.25 seconds | | 11 | 86 | "I feel a little tingling in the back of my neck." |
| 10 : 27.35 seconds | 108/66 | | | |
| | Injection finished. | | | |
| 10 : 28.30 seconds | 106/68 | 11 | 86 | |

Patient complained of severe itching and sat up in bed scratching himself violently on the face, which was flushed. He complained of that tingling sensation over this area.

A brilliant red flush was now noted over the face, neck and upper part of the chest anteriorly. This did not extend to the arms or the lower part of the chest and was not noted elsewhere. Patient complained of a terrific itching over the red area; this was especially marked at the back of the neck. He rubbed and scratched furiously for about five minutes and for the rest of the experiment the itching was present, but in a lesser degree.

10 : 43 a. m. : Reflexes of both knees and ankles were tested by Dr. Stanley Cobb of Boston, who expressed the opinion that they seemed active enough and appeared practically normal.

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 10:48 a. m.: Fifth dosage of 4 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:49.01 seconds | 104/64 | | 76 | |
| 10:49.43 seconds | 102/64 | | | |
| 10:49.50 seconds | | | | Patient lay with closed eyes and when asked about his thoughts said: "I was just thinking about McCarthy, another patient here, that's all." |
| 10:50.21 seconds | 102/62 | | 78 | |
| 10:50.45 seconds | | | | "How do you feel?" "All right. My nerves are all right. Yes, I could stand another shot." |
| 10:50.55 seconds | 102/64 | | | |
| 10:51.55 seconds | 102/62 | | 80 | |
| Injection finished. | | | | |
| 10:52.55 seconds | 102/64 | | 78 | |
| Patient scratched the palm of his right hand. He said he was hungry. "No, the weight in my stomach has gone. That lasted only a very few minutes. It was a depressed feeling down there, something heavy down there." | | | | |
| 10:58 a. m.: Sixth dosage of 4 grains of morphine sulphate, intravenously, begun. | | | | |
| 10:58.20 seconds | 104/64 | | | |
| 10:59.02 seconds | 102/64 | | 76 | |
| 10:59.25 seconds | | | | "I feel all right now and have for the last ten minutes. I would like a hypo in the muscle. I will wait for fifteen minutes though." |
| 10:59.42 seconds | 102/64 | | | |
| 11:00.15 seconds | 104/66 | | 80 | |
| 11:00.40 seconds | | | | Felt kind of dry in the mouth. (He asked for a glass of water.) "My nose is all free and everything now. I am not coughing and my stomach is all right. Yes, I am comfortable now." |
| 11:01.05 seconds | 102/64 | | | "No, I am not drowsy" (although patient spoke slowly). "Warm?" "Yes, but not too warm." |
| 11:01.59 seconds | 102/64 | | 80 | |

| Time | Blood Pressure | Respiration | Pulse Rate | Remarks |
|---|---|---|---|---|
| 11:02.43 seconds | 102/62 | | | Felt a tingling in the jaws —just an itching back there, that was all. |
| | Injection finished. | | | |
| 11:03.14 seconds | 102/62 | | 80 | |

Patient did not complain of a headache but said that he would like a hypodermic injection into the muscle because "you usually get one when you get it in the vein like this, and it goes so slow." He denied that he had a headache now, however.

### COMMENT AND LITERATURE

We have demonstrated in the foregoing experiments that in the addicts who acted as subjects morphine was tolerated in far greater amounts than those required to prevent withdrawal symptoms. The intramuscular dosages were three, four and six times the amounts usually given, while the intravenous dosages were six, seven and nine times the usual quantities. In the two cases in which the regular dosage was abruptly withdrawn for a period of forty-eight hours, the tolerance for intravenous doses was still present, in one case 20 grains (1.3 Gm.) being administered in fifty-six minutes and in the other 11 grains (0.7 Gm.) in one hour and sixteen minutes. These additional quantities did not prolong the period before the addict again requested his drug. This is contrary to the statement of Bishop,[2] who claimed that additional quantities prolonged proportionately the interval between demands for the drug.

The physiologic changes brought about by these additional amounts taken as a whole may be regarded as practically negative. In case 26-21, there was an increase in the venous oxygen of the blood drawn from the median basilic vein following administration of these large quantities compared to that present while the addict was receiving his regular dosage and also following the abrupt withdrawal period. All the intravenous experiments were accompanied by a distinct flushing of the face, neck and upper part of the chest anteriorly. All the addicts complained of feeling more or less warm, as well as "loaded." Careful studies of the blood pressure and pulse rates did not reveal any essential differences accompanying the sensations described by the addict.

The question naturally follows, "What has become of this additional morphine and why has it been ineffective in producing any pronounced physiologic changes? Failure of absorption cannot be considered, as in five experiments the drug was given intravenously, most of it having

2. Bishop, Ernest S.: The Narcotic Drug Problem, New York, The Macmillan Company, 1921, p. 33.

left the circulation at the conclusion of the injections, as Dr. Balls was able to find less than 1 mg. in 25 cc. of blood. Failure to bring about any obvious changes in the respiration and the absence of any tendency to sleep on the part of the addicts prove the ineffectiveness of these large doses in bringing about the normal pharmacologic action of morphine on the central nervous system. Several conclusions are to be considered in this respect: First, the additional amounts have no effect on the central nervous system, the latter having become tolerant to large as well as to small amounts; second, the additional amounts must be either rapidly excreted or removed from the blood by tissues other than those of the central nervous system and destroyed, or chemically bound and made inert, and slowly returned to the blood for excretion. The latter conclusion is that of Terruchi and Kai,[3] who worked with rabbits.

Faust[4] attributed tolerance in dogs addicted to morphine to a mechanism developed in them which rapidly destroyed the morphine, as he was unable to recover any in their feces. Rubsamen[5] agreed with Faust that there was increased destruction but was able to recover sufficient morphine from tolerant rats to kill nontolerant rats. Rubsamen concluded, then, that there must be not only an increased destruction but also an increased tolerance on the part of the central nervous system. Terruchi and Kai[3] recovered quantities of morphine from the muscles and small amounts from the liver and brain of addicted rabbits. In their conclusions, Terruchi and Kai stated: "We venture to conclude that the morphinism is due to the acquired power of the living organism to destroy morphine, and to excrete it besides the augmented power to reserve it in a large amount by the muscles, so that even though a large amount of it should be introduced into the body all at once it can be prevented from immediately attacking the central nervous system."

In consideration of the work just cited and our own experiments, we believe that these large amounts of morphine introduced into the circulation are promptly removed by the muscles, so that only small quantities are available for action on the central nervous system. Having once been removed by the muscles, the morphine must have been destroyed or returned slowly to the circulation in small quantities, as Dr. Balls was able to detect only the slightest amounts in the blood. The regular return of craving for the drug on the part of the addicts within a period of three or four hours would indicate, on the other

3. Terruchi, Yutaka; and Kai, Sotaro: On the Fate of Morphine Which Has Been Injected into the Animal Body, J. Pharm. & Exper. Therap. **31**:177, 1927.

4. Faust, E. S.: Ueber die Ursachen der Gewöhnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **44**:217, 1900.

5. Rubsamen, W.: Experimentelle Untersuchungen über die Gewöhnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **59**:227, 1908.

hand, a rather rapid destruction in the muscles, or a quick elimination. Using the hypothesis of Terruchi and Kai,[3] one can find a plausible explanation for the frequency with which the addict increases the amounts required for his need. With the development of a mechanism in the muscles for the removal of morphine from the circulation, one can conceive of it becoming so effective as to leave an insufficient quantity for action on the central nervous system and the addict consequently increasing his regular dosage.

We believe from indirect evidence and the behavior of addicts in general that the quantity of morphine required to prevent the appearance of withdrawal symptoms to be considerably less than is normally used by them. This evidence is based on the following observations. All of our patients who have taken a cure either in our ward or in other institutions and who have had a relapse always begin the use of the drug again in small quantities, rarely more than from ¼ to ½ grain (0.01 to 0.03 Gm.) at each injection. These amounts are ample to restore them to what they consider their normal feeling and also to give them the so-called "kick." These amounts suffice for various lengths of time, and as soon as the "kick" is no longer obtained the addict begins increasing the amounts taken. Our experience with reducing the doses results in little complaint on the part of the patient regardless of the amounts being used or the speed of reduction until the point is reached where the individual dosages are reduced from ½ grain to lower amounts. It is at this point that the addict becomes exceedingly difficult to handle and presents withdrawal symptoms.

Another phase in this problem of the amounts required to prevent withdrawal symptoms is the existence of two more or less ill defined groups of addicts which they themselves classify as "users" and "hogs." One also encounters two mental states following the use of morphine in which the addicts say that they feel "normal" or that they feel "loaded." The group of so-called "users" are able to get along nicely over a period of years on small daily dosages, but nevertheless require these small dosages to prevent withdrawal symptoms. The other group consists of those who are not content to feel normal but who are constantly desirous of being "loaded," and it is the persons in this group who continually increase the amounts taken and are forced to take a cure, after which they are able to begin all over again with small amounts.

Our experience with addicts and all cures, including "cold turkey," [6] is that at the end of the week to ten days all acute withdrawal symptoms have disappeared. The addict is now able to satisfy his craving as well as to derive a "kick" with dosages as low as from ⅛ to ¼ grain (8 to 16 mg.).

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6. Abrupt withdrawal without the substitution of any drug.

If ignorant of this small requirement, the addict may take his regular dosage and suffer serious results and even death. One of our patients died suddenly following discharge from the hospital after taking an injection of the same quantity used before the cure was taken. These sudden deaths are not infrequent, according to addicts, although the reliability of their statements must always be questioned.

It would appear, then, on the basis of the conclusions of Terruchi and Kai that within a week or ten days the muscles lose their ability to remove the drug from the circulation, and that small quantities will again suffice to give the addicts their feeling of normality or "kick." Furthermore, the foregoing theory still being used as an explanation, the ability of the muscles to remove the morphine from the circulation is not brought into play until dosages in excess of those required to prevent withdrawal symptoms are used.

This application of the theory of Terruchi and Kai does not, however, offer any explanation as to the cause of the appearance of the withdrawal symptoms nor the presence of the craving for the drug after the acute withdrawal symptoms have disappeared. Marme [7] attributed the cause of the withdrawal symptoms to the presence of pseudomorphine and believed that additional amounts of morphine were required to counteract the presence of the pseudomorphine. This work has been criticized by Donath,[8] Stark,[9] Marquis,[10] Toth [11] and Gioffredi,[12] in a review of the literature on tolerance and withdrawal phenomena by Du Mez.[13] Before accepting any explanations or theories as to what has happened to the morphine, one should know whether these large quantities are rapidly excreted in human addicts, by what channels, and whether morphine is still being excreted while withdrawal symptoms are present. Such experiments are planned and will be carried out as our next step in the study of opium addiction.

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7. Marme, W.: Untersuchungen zur acuten und chronischen Morphin-Vergiftung; Deutsche med. Wchnschr. **9**:197, 1883.

8. Donath, J.: Das Schicksal des Morphins im Organismus, Arch. f. d. ges. Physiol. **38**:528, 1886.

9. Stark, E.: Untersuchungen uber die Gewohnung des thierischen Organismus an Gifte; Inaug. Diss., Erlangen, 1887; cited by Faust, Arch. f. exper. Path. u. Pharmakol. **44**:225, 1900.

10. Marquis, E. P.: Ueber den Verbleib des Morphins im thierischen Organismus, Pharm. Ztschr. f. Russland **35**:549, 1896.

11. Toth, L.: Bemerkungen zur Erklarung der chronischen Morphiumintoxikation, Schmidt's Jahrb., 1891, vol. 229, p. 135.

12. Gioffredi, Carlo: Recherches ulterieures sur l'immunisation pour la morphine, Arch. ital. de biol. **31**:398, 1899.

13. Du Mez, A. G.: Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J. A. M. A. **72**:1069 (April 12) 1919.

## CONCLUSIONS

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignificant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood, and the behavior of the addict.

The intravenous administration of 20 grains and 11 grains to two different addicts following a forty-eight hour withdrawal period also failed to produce any significant physiologic changes or changes in behavior after fifty-six minutes and one hour and sixteen minutes, respectively.

Analyses of the blood for morphine showed the presence of less than 1 mg. per 25 cc. of blood, indicating its rapid removal following the completion of the injection.

# IX. WATER BALANCE STUDIES DURING THE ADMINISTRATION AND THE WITHDRAWAL OF MORPHINE

Abrupt withdrawal of morphine from human addicts is practically always associated with loss of weight during the manifestation of the so-called "withdrawal symptoms." During this period, the addicts invariably refuse to take any nourishment, their water intake is practically negligible and increased perspiration is noted. It is the object in this paper to report the results of our studies of water balance in five addicts, as well as in three normal persons, given the same diet, in order to determine whether the loss of weight is due entirely to inanition, or in part to an additional loss of water as the result of increased metabolism.

## METHODS

Water balance was estimated by the method of difference of weight. The diet employed consisted of a modified Folin[1] diet prepared each morning, the ingredients used being: eggs, whole milk, cream, malted milk, coffee, vanilla, Welch's grape juice and sugar, as well as 7 Gm. of salt and 25 Gm. of candy, in addition to water. These substances were prepared in various combinations, and administered in the same quantities, at the same hour each day, throughout the experiment. The normal subjects, first-year medical students in the School of Medicine of the University of Pennsylvania, who were taking their final examinations in anatomy and chemistry, were able to continue this regimen throughout the seven days of the experiments. The addicts succeeded in retaining all food administered while they were receiving their drug. Only two, however, accepted and retained the food during the forty-eight hour withdrawal of morphine, and one of these refused the additional water that was included in the day's proffer of food and drink. In the table is given the number of calories administered per day together with the amounts of protein, carbohydrate and fat from which the caloric intake was calculated.[2]

The subjects were weighed exactly at 9 o'clock each morning, on a silk scale of the type proposed by Benedict and Root,[3] the scale weighing accurately to within 10 Gm. The subjects were required to remove all clothing following the weighing, the clothing then being weighed separately and deducted from the total weight obtained. Before being weighed, all subjects were required to pass their urine and defecate if possible. The last administration of a food mixture was given at 3 a. m., the last administration of water, at 6 a. m. Dietetic scales were used to measure to within a gram the amount of food and water taken.

All urine, feces, vomitus and blood were collected and weighed on a scale in the ward, with an accuracy of within 1 Gm. The total collections were again

1. Folin, Otto: Approximately Complete Analyses of Thirty Normal Urines, Am. J. Physiol. **13**:44, 1905.

2. Lusk, Graham: The Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 1923, p. 42.

3. Benedict, F. G., and Root, H. L.: Insensible Perspiration: I. Its Relation to Human Physiology and Pathology, Arch. Int. Med. **38**:1 (July) 1926.

reweighed in the laboratory as a check on the amounts obtained in the ward. Toluene was used to preserve the urine.

The Kjehldahl method was used for the determination of the amount of nitrogen in the urine and dried feces. The amount of uric acid of the urine was determined by the method of Benedict and Franke.[4] The Folin colorimetric method[5] was used to determine the amount of creatinine of the urine. We are indebted to Austin and Sunderman[6] for the method of calculating the water balance.

Throughout this study we have made an arbitrary allowance for maximal error for each measurement and estimate. This allowance for error is designated in text and table by the symbol ± and must not be confused with probable error or other statistical function.

*Calculation of Water Balance.*

Measured intake (grams):

(1) $I = (\text{food} + \text{beverage} + \text{enema in grams}) \pm 2$ per cent.

Measured intake of water (grams):

(2) $W_i = (\text{water of food estimated from tables [but not the water of oxidation]} + \text{beverage} + \text{enema}) \pm 2$ per cent.

Water of oxidation of food intake (grams):

(3) $W_{ox.\ i} = (0.413\ P_i + 0.555\ C_i + 1.071\ F_i) \pm 2$ per cent in which $P_i$, $C_i$ and $F_i$ are the grams of protein, carbohydrate and fat in the intake. The amount of water formed by oxidation is taken from Magnus-Levy's calculations that 100 Gm. of protein give 41.3 Gm. of water, 100 Gm. of carbohydrate give 55.5 Gm. of water and 100 Gm. of fat give 107.1 Gm. of water.

Total water intake (grams):

(4) $W_{ti} = W_i + W_{ox.i.}$

Measured output (grams):

(5) $O = (\text{urine} + \text{feces} + \text{sputum} + \text{blood removed}) \pm 2$ per cent.

Measured water output (grams):

(6) $W_o = (W_u + W_{fec} + W_{sp} + W_{bl}) \pm 2$ per cent.

Daily change in weight (grams):

(7) $\Delta Wt = (\text{initial weight} - \text{final weight}) \pm 20$ Gm. for the period. In the estimation of mean increment per day, this allowance for error is divided by the number of days in the period.

Weight loss through skin and lungs (grams):

(8) $-\Delta Wt_{s.l.} = -\Delta Wt - (O - I)$.

Weight loss due to excess of $CO_2$ in grams over $O_2$ in grams:

(9) $(CO_2 - O_2) = 75 \pm 75$.

This range is taken as sufficiently inclusive to cover any reasonable variation in total metabolism and respiratory quotient.

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4. Benedict, S. R., and Franke, Elizabeth: A Method for the Direct Determination of Uric Acid in Urine, J. Biol. Chem. **52**:387, 1922.

5. Folin, Otto: Beitrag zur Chemie der Kreatinins und Kreatins im Harne. Ztschr. f. phys. Chem. **41**:223, 1904.

6. Sundermain, F. W., and Austin, J. H.: Studies of Serum Electrolytes: VI. Water Metabolism in Pneumonia, Am. J. M. Sc. **179**:167 (Feb.) 1930.

Water loss through skin and lungs, neglecting the solids of the sweat, which are assumed to be less than 0.5 per cent of the water loss (grams):

(10) $W_{s.l.} = (-\Delta Wt_{s.l.} - [CO_2 - O_2]) \pm$ error (table may be seen here).

Total water output (grams):

(11) $W_{t.o.} = (W_o + W_{s.l.}) \pm$ error (table).

Absolute daily water balance:

(12) $WBal_{abs.} = (W_{t.i.} - W_{t.o.}) \pm$ error (table).

## RESULTS

Examination of the table giving the data relative to the water metabolism shows:

1. The three controls and all the addicts, except addict 3, were in water balance within our allowance for error in their first periods, while receiving the drug. Addict 3 in the first period, while receiving the drug, suffered a water loss.

2. During the two or three days of withdrawal of morphine, a definite and usually great negative water balance occurred. This occurred in two subjects, addicts 1 and 2, without diminution in the intake of food, although in the latter diminution in fluid intake accounted for half of the loss. Both, however, showed increased water output. In the other three subjects, the diminished intake of food and water was the outstanding feature and it gave rise to a negative water balance in spite of some diminution in the water excretion.

3. In the final periods during which the three addicts were studied, after resumption of the drug, the food and water intake was approximately as in the first period. In two, addict 4 and addict 5, there was definite water retention; in neither addict 1 nor addict 4, however, did it in three days compensate for the previous loss.

4. When the water loss from skin and lungs is considered as a fraction of the total water loss through skin, lungs and urine, two addicts, nos. 1 and 3, exhibited initially a high loss of water through skin and lungs as compared with the controls. One can also recognize in three of the addicts, nos. 2, 4 and 5, a relatively greater loss through the skin and lungs during the withdrawal period.

The explanation of this disturbance in the water balance during the period of withdrawal, had we only the data on addicts 3, 4 and 5, would naturally be the loss of water associated with inanition. This explanation hardly serves for the loss in addicts 1 and 2, unless we postulate an increased metabolism in these subjects during withdrawal. That such may well be the case seems not wholly improbable in view of the restlessness and nervousness of the individual patient during the withdrawal of the drug.

*Summary of Water Balance Studies in Normal Subjects and in Human Opium Addicts During Administration, Withdrawal and Readministration of Morphine**

| Subject | Dates | Days in Period | Treatment | Change in Weight, Gm. | Food Intake: Protein, Gm. | Food Intake: Carbohydrates, Gm. | Food Intake: Fat, Gm. | Food Intake: Calories | Nitrogen Output, Urine and Feces, Gm. | Uric Acid in Urine, Mg. | Water of Oxidation of Food, Gm. | Total Water Intake, Gm. | Water Output of Urine, Gm. | Water Output of Skin and Lungs, Gm. | Total Water Output, Gm. | Water Balance, Gm. | $\frac{W_{s.l.}}{W_u + W_{s.l.}}$ | Creatinine Coefficient, Urine |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Control 1 (K. L.) | 6/ 1 to 6/ 7/28 | 7 | None | — 100 ± 3 | 102 | 235 | 141 | 2,750 | 16.6 | 441 | 323 ± 6 | 2975 ± 60 | 1885 ± 38 | 1080 ± 98 | 3059 ± 138 | — 84 ± 198 | 0.36 ± .04 | 9.51 |
| Control 2 (J. H.) | 6/ 2 to 6/ 7/28 | 6 | None | — 38 ± 3 | 102 | 235 | 141 | 2,750 | 16.0 | 464 | 323 ± 6 | 2982 ± 60 | 1720 ± 34 | 1231 ± 103 | 3007 ± 138 | — 25 ± 198 | 0.42 ± .06 | 9.94 |
| Control 3 (H. M.) | 6/ 2 to 6/ 7/28 | 6 | None | — 39 ± 3 | 102 | 235 | 141 | 2,750 | 16.2 | 565 | 322 ± 6 | 2982 ± 60 | 1830 ± 36 | 1118 ± 101 | 3003 ± 138 | — 21 ± 198 | 0.38 ± .05 | 8.90 |
| Addict 1 (M. C.) | 3/23 to 3/27/28 | 5 | With drug | — 85 ± 4 | 102 | 196 | 138 | 2,575 | 13.2 | 465 | 299 ± 6 | 2445 ± 49 | 1083 ± 22 | 1111 ± 99 | 2521 ± 128 | — 76 ± 177 | 0.51 ± .05 | 8.08 |
| | 3/28 to 3/29/28 | 2 | No drug | - 575 ± 10 | 102 | 196 | 138 | 2,575 | 16.6 | 964 | 299 ± 6 | 2414 ± 48 | 1367 ± 27 | 1468 ± 104 | 2942 ± 133 | — 528 ± 181 | 0.51 ± .05 | 8.36 |
| | 3/30 to 4/ 1/28 | 3 | With drug | + 5 ± 7 | 102 | 196 | 138 | 2,575 | 16.5 | 535 | 299 ± 6 | 2570 ± 51 | 1340 ± 27 | 985 ± 101 | 2569 ± 133 | + 1 ± 184 | 0.42 ± .06 | 8.28 |
| Addict 2 (V. W.) | 3/23 to 3/27/28 | 5 | With drug | + 89 ± 4 | 101 | 196 | 138 | 2,550 | 15.8 | 428 | 299 ± 6 | 2442 ± 49 | 1302 ± 26 | 878 ± 99 | 2333 ± 128 | + 109 ± 177 | 0.40 ± .06 | 7.80 |
| | 3/28 to 3/29/28 | 2 | No drug | - 1121 ± 10 | 101 | 180 | 138 | 2,500 | 16.9 | 900 | 299 ± 6 | 1977 ± 40 | 1337 ± 27 | 1593 ± 96 | 3077 ± 125 | —1100 ± 165 | 0.54 ± .06 | 7.07 |
| Addict 3 (W. C.) | 2/27 to 3/ 1/28 | 4 | With drug | — 539 ± 5 | 102 | 178 | 135 | 2,450 | 16.7 | ... | 290 ± 6 | 2747 ± 55 | 820 ± 16 | 2013 ± 113 | 3225 ± 135 | — 478 ± 190 | 0.71 ± .07 | |
| | 3/ 2 to 3/ 4/28 | 3 | No drug | - 1494 ± 7 | 30 | 52 | 42 | 750 | 19.1 | ... | 87 ± 2 | 1406 ± 28 | 707 ± 14 | 2093 ± 95 | 2856 ± 110 | —1450 ± 138 | 0.75 ± .06 | |
| Addict 4 (W. W.) | 5/ 6 to 5/ 8/28 | 3 | With drug | — 83 ± 7 | 104 | 235 | 141 | 2,775 | 15.4 | 361 | 325 ± 6 | 3163 ± 63 | 1882 ± 38 | 1036 ± 100 | 3250 ± 145 | — 87 ± 208 | 0.36 ± .05 | 9.00 |
| | 5/ 9 to 5/10/28 | 2 | No drug | —1004 ± 10 | 1.5 | 1.5 | 19 | 200 | 14.2 | 352 | 175 ± 4 | 1697 ± 34 | 1279 ± 26 | 1240 ± 91 | 2518 ± 119 | —1339 ± 153 | 0.49 ± .05 | 6.71 |
| | 5/11 to 5/13/28 | 3 | With drug | + 690 ± 7 | 104 | 235 | 141 | 2,775 | 17.4 | 352 | 325 ± 6 | 2863 ± 57 | 1308 ± 26 | 787 ± 112 | 2162 ± 139 | + 701 ± 196 | 0.38 ± .08 | 8.20 |
| Addict 5 (S. Z.) | 5/ 6 to 5/ 8/28 | 3 | With drug | — 149 ± 7 | 104 | 235 | 141 | 2,775 | 15.9 | 503 | 325 ± 6 | 2860 ± 57 | 1976 ± 40 | 948 ± 97 | 3016 ± 139 | — 156 ± 196 | 0.32 ± .04 | 7.48 |
| | 5/ 9 to 5/10/28 | 2 | No drug | — 908 ± 10 | 49 | 68 | 125 | 1,675 | 14.3 | 604 | 163 ± 3 | 1672 ± 33 | 1257 ± 25 | 925 ± 87 | 2503 ± 118 | — 831 ± 151 | 0.42 ± .05 | 6.11 |
| | 5/11 to 5/13/28 | 3 | With drug | + 809 ± 7 | 104 | 235 | 141 | 2,775 | 16.3 | 377 | 325 ± 6 | 2863 ± 57 | 1187 ± 24 | 832 ± 114 | 2078 ± 139 | + 785 ± 196 | 0.41 ± .08 | 6.61 |

* Each calculation represents the mean per day for the period of study.

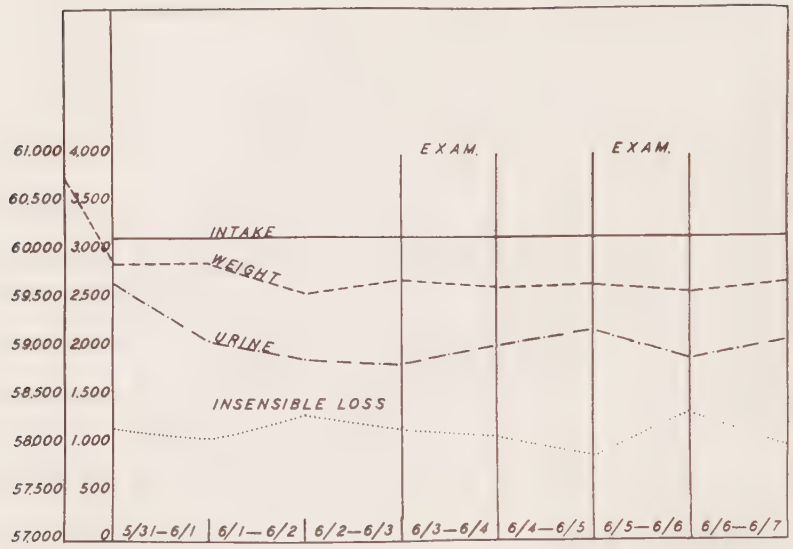


Chart 1.—Graphic representation of the daily intake of food, change in weight, urine output and invisible water loss of control 2. The ordinates represent grams.

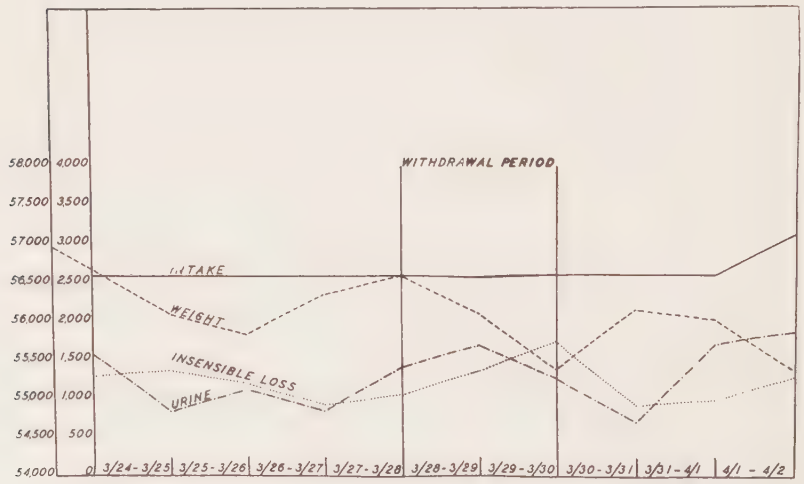


Chart 2.—Graphic representation of the daily intake of food, change in weight, urine output and insensible water loss of addict 1. The ordinates represent grams.

The output of nitrogen, as shown in the short periods studied, showed little or no change even when during the two days of withdrawal of morphine the food intake was curtailed. The output of uric acid shows in both addicts whose food intake during withdrawal was maintained, a definite rise.

All addicts during the first twenty-four hours of withdrawal showed a relative increase in the output of urine followed by a decided fall during the second twenty-four hours of this period. Water loss through skin and lungs, on the other hand, showed a relative increase during the second twenty-four hours compared with that during the initial twenty-four hours of withdrawal.

## COMMENT

From the data available one can recognize a loss of weight and water during withdrawal. The tendency in three of the subjects to reduce the intake of food and fluid during the withdrawal period was undoubtedly a major factor in bringing this about. In two other subjects, whose food intake remained the same, the loss of weight was possibly an evidence of increased metabolism which may have had no further cause than the nervous restlessness of the individual patient at this time. That there was any more specific effect of the withdrawal of the drug on the water metabolism seems from the data obtained unlikely, but it cannot be absolutely excluded. To attempt a further answer by a study of withdrawal with the addict on a much higher level of caloric intake seems hopeless because of the aversion during withdrawal to even the moderate diet used in this study.

A marked increase in excretion of uric acid detected in addicts 1 and 2 with a constant diet, is noted in the table. All other addicts who served as subjects failed to maintain this constant intake. Studies of the uric acid of the blood in four other cases during withdrawal, however, failed to show any significant changes. Schubel [7] found an increased elimination of purine base and phosphoric acid during abrupt withdrawal in dogs, and attributed this to a sudden alteration in the central nervous system which he claimed took place following withdrawal of the drug. Sollier [8] attributed the symptoms accompanying withdrawal to marked alterations brought about in glands, particularly the endothelial cells, when morphine is no longer given.

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7. Schubel, Konrad: Stoffwechselversuche an Hunden während der Gewohnung an Morphin und während des Morphinhungers, Arch. f. exper. Path. u. Pharmakol. **88**:1, 1920.

8. Sollier, P.: La démorphinisation. Mécanisme physiologique. Conséquences au point de vue thérapeutique, Presse méd., April 23 and July 8, 1898.

The medical students who acted as normal subjects in these experiments were selected with a knowledge of their tendency to worry during examination. It is significant to know that these men retained their normal weight throughout the experiment, and failed to show a negative water balance or any increase in frequency or amount of urine on the two days on which the final examinations were given.

## CONCLUSIONS

Abrupt withdrawal of morphine in a series of human addicts to opium resulted in a negative water balance and, in two of these subjects, an increased elimination of uric acid. The negative water balance was most likely due to failure to take sufficient food and water, although increased loss of water from increased metabolism cannot be entirely excluded, particularly in view of the restlessness of these subjects during withdrawal.

The control subjects, three medical students taking their first year final examinations, failed to show a negative water balance, any increase in frequency of urination or in twenty-four hour output, or any loss of weight on the days of the final examinations.

# X. THE EXCRETION OF MORPHINE BY HUMAN ADDICTS

The relation between the capacity of the animal body to destroy morphine and its power of developing tolerance to the drug following repeated dosage has been of interest to pharmacologists for many years. Recent study with the aid of improved chemical methods indicates that Faust's [1] conclusion, that a direct, casual relationship between the two phenomena exists, is incorrect. It seemed important to collect from human material such data as might bear on this subject. The study here reported concerns the excretion of morphine by human addicts; the difference between the amounts of morphine administered and those excreted is to be regarded as a measure of morphine destroyed.

While it is well known from the early observations of Kauzmann,[2] Vogt,[3] and Jacques [4] that morphine is eliminated in the urine and feces of human addicts, its quantitative excretion in these channels has, to our knowledge, not been studied. In the subjects whom we have studied it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively. In addition to observations on the (healthy) subjects of uncomplicated addiction, we had the opportunity of measuring the elimination of morphine, on constant dosage, during the periods of fever, crisis and convalescence in one addict who was acutely ill with pneumonia.

## METHODS AND PROCEDURE

As soon as possible after admission the predetermined morphine regimen was established. The daily dosages of morphine chosen were 15, 30 and 60 grains (0.97, 1.94 and 3.89 Gm.), and a period of four days was ample to establish any one of these levels, regardless of the amounts which had been taken before admission or the form of the drug used. Experimental periods usually lasted for five days, although one case was studied for only three days and another for four days. No attempt was made to control the diet, nor were any other drugs administered except an occasional saline cathartic to obtain a bowel movement.

Morphine in urine was determined by extraction with chloroform-alcohol solvent, purification through further extractions and final precipitation with

1. Faust, E. S.: Ueber die Ursachen der Gewohnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **44**:217, 1900.

2. Kauzmann: Beiträge für den gerichtlich chemischen Nachweis des Morphins und Narkotins in thierschen Flussigheiten und gemehen, Inaug. Dissert., Dorpat, 1868. Cited by Faust (footnote 1, p. 223).

3. Vogt: Arch. d. Pharm. **7**:23 (July) 1875.

4. Jacques: Thèse Bruxelles, 1880; Essai sur localization des alcoloides dans le foie, cited by Faust (footnote 1, p. 224).

silicotungstic acid.[5] When the quantity of morphine in the final extract was less than 10 mg., it was estimated colorimetrically by the diazo-reaction.[6]

The suitability of this procedure for human material was shown by a series of control experiments. From 100, 200, 250 and 280 cc. volumes of normal urine, analyzed gravimetrically, recoveries of added morphine were from 92 to 97.7 per cent. The morphine silicotungstate yielded, after ignition, from 70 to 70.3 per cent of oxide residues, an indication of the almost complete purity of the morphine precipitate. Similar controls containing no morphine showed negligible turbidity with silicotungstic acid. Colorimetric control experiments gave from 98 to 100 per cent recoveries of added morphine, with satisfactory blanks. These results were obtained only after meticulous attention to detail, as described by one of us (W. A. W.)[7] in a study of the elimination of morphine in dogs. The numerous possibilities of error in morphine analysis made it necessary to check and recheck every step in the procedure at frequent intervals.

Many of the specimens of urine were analyzed both colorimetrically and gravimetrically. Typical results shown in table 1 indicate the consistency of the two methods.

Feces, after preliminary acidification and evaporation over the steam bath, were analyzed as previously described.[5] Results on control determinations were variable and unsatisfactory. Hence, the figures presented for fecal excretion are hardly more than qualitative indications that a relatively small amount of morphine appears in the feces.

## RESULTS AND COMMENT

Table 2 contains the results of the quantitative excretion of morphine in the urine and feces of a series of addicts receiving 15, 30 or 60 grains per twenty-four hours. Sixteen studies were made on ten different patients. One patient (case 3-29) was studied on all three levels: he eliminated 7.9, 8.2 and 10.3 per cent, respectively, in the urine. Cases 10-29 and 2-29 were each studied on two different levels. The patient in case 10-29 eliminated 8.6 per cent in the urine while receiving 30 grains, and 7.7 per cent on a 60 grain level. Likewise in case 2-29 there was little variation in the percentage of morphine eliminated. While receiving 15 grains he excreted 10.1 per cent, and while receiving 60 grains, 12.2 per cent.

Case 6-29 was studied on the same level of 30 grains at two different intervals, with the elimination of 8.8 and 9.5 per cent of the morphine administered.

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5. Balls, A. K., and Wolff, W. A.: The Determination of Morphine, J. Biol. Chem. **80**:379 (Dec.) 1928.

6. Lautenschlager, L.: Arch. d. Pharm. **257**:13, 1919. Plant, O. H., and Pierce, I. H.: Excretion of Morphine During Gradually Produced and Prolonged Tolerance to Morphine in Dogs, J. Pharmacol. & Exper. Therap. **31**:212 (June) 1927.

7. Wolff, W. A.: The Elimination of Morphine in Dogs, to be published.

Five patients who were maintained on 15 grains (0.97 Gm.) daily varied from 6.5 to 10.1 per cent of excretion. Urinary excretion of morphine for seven patients on a constant dosage of 30 grains ranged from 8.2 to 12.9 per cent. Morphine recovered from the urine of four patients receiving 60 grains per day varied from 7.7 to 12.2 per cent. It may be noted that the percentage of morphine eliminated in the feces analyzed never exceeded one-fourth the urinary percentage. Absolute values were too uncertain and variable to justify general conclusions.

The results obtained in the foregoing experiments on healthy addicts show that regardless of the amounts taken, the fraction eliminated in the urine is remarkably constant. Averages of the percentage of urinary excretion on the 60, 30 and 15 grain dosages amounted to 10.7, 9.8 and 8.7 per cent, respectively. The fraction eliminated bears no relation to height, weight, volume of urine or length of addic-

TABLE 1.—*Comparative Results of Colorimetric and Gravimetric Methods in Analysis of Urine for Morphine*

| Case | Colorimetric Method, Mg. per 100 Cc. | Gravimetric Method, Mg. per 100 Cc. |
|---|---|---|
| 5–29 | 4.7 | 4.1 |
| 12–29 | 32.7 | 32.0 |
| 4–29 | 6.1 | 7.8 |
| 10–29 | 8.2 | 9.3 |
| 10–29 | 15.0 | 15.3 |
| 3–29 | 9.2 | 8.4 |
| 3–29 | 22.0 | 18.8 |

tion, but is directly proportional to the quantity administered. These results show clearly that in human addicts the amount of morphine destroyed is proportional to the amount absorbed. Despite the existence of mechanisms for the disposal of morphine, there must still be present in the addict an increased tissue tolerance, since the patients receiving 60 grains a day were eliminating in the urine approximately 6 grains (0.388 Gm.), and those on 30 grains approximately 3 grains (0.194 Gm.).

The lethal dose of morphine for man is not definitely stated in textbooks of pharmacology. Kunkel [8] quoted the minimal lethal dose as 1½ grains (0.097 Gm.), but added that under favorable circumstances a person might recover from 15 grains. He regarded, however, the prognosis from a dosage of over 4 grains (0.259 Gm.) as decidedly unfavorable. Sollmann [9] stated that the lethal dose ranges

8. Kunkel, A. J.: Handbuch de Toxikologie, part 2, Jena, Gustav Fischer, 1901, p. 803.

9. Sollmann, Torald: A Manual of Pharmacology, ed. 3, Philadelphia, W. B. Saunders Company, 1926, p. 300.

between 3 and 6 grains, but mentioned one case of recovery from 60 grains. He also regarded the prognosis unfavorable when the dosage was more than 4 grains.

Table 3 and chart 1 contain the results of the analysis of urine collected at two hour intervals for the first twelve hours, four hour intervals for the second twelve hours and a final six hour period, during thirty hours of abrupt withdrawal. In each case the last hypodermic injection of morphine sulphate given was 5 grains (0.324 Gm.).

TABLE 2.—*Data Obtained from Patients During Periods of Addiction*

| Case | Age, Years | Period of Study, Days | Average Weight | | Average Daily Urine for Period, Cc. | Daily Administration of Morphine | | Average Daily Excretion | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Urine | | | Feces, per Cent |
| | | | Pounds | Kg. | | Gm. | Mg. | Grains | Mg. | Per Cent | |
| 1-29 | 36 | 5 | 189 | 87.0 | 1,700 | 15 | 972 | 1.50 | 97 | 10.0 | 2.2 |
| 2-29 | 32 | 3 | 133 | 61.3 | 1,466 | 15 | 972 | 1.51 | 98 | 10.1 | 3.0 |
| 3-29 | 36 | 5 | 136 | 62.6 | 865 | 15 | 972 | 1.16 | 76 | 7.9 | ... |
| 4-29 | 39 | 5 | 113 | 52.0 | 1,217 | 15 | 972 | 1.17 | 77 | 7.9 | ... |
| 5-29 | 46 | 5 | 133 | 61.3 | 1,424 | 15 | 972 | 0.97 | 63 | 6.5 | ... |
| 6-29 | 35 | 5 | 122 | 56.2 | 2,332 | 30 | 1,944 | 3.24 | 168 | 8.8 | ... |
| 7-29 | 39 | 5 | 156 | 71.8 | 1,652 | 30 | 1,944 | 4.04 | 210 | 10.6 | 3.5 |
| 8-29 | 40 | 5 | 120 | 55.3 | 869 | 30 | 1,944 | 3.88 | 252 | 12.9 | 1.7 |
| 3-29 | 36 | 5 | 138 | 63.5 | 1,602 | 30 | 1,944 | 2.46 | 160 | 8.2 | 1.0 |
| 10-29 | 30 | 4 | 154 | 70.9 | 1,896 | 30 | 1,944 | 2.57 | 167 | 8.6 | 3.3 |
| 6-29 | 35 | 5 | 126 | 58.0 | 1,808 | 30 | 1,944 | 2.83 | 184 | 9.5 | ... |
| 9-29 | 34 | 5 | 150 | 69.1 | 2,841 | 30 | 1,944 | 3.14 | 204 | 10.5 | ... |
| 10-29 | 30 | 5 | 156 | 71.8 | 1,976 | 60 | 3,888 | 4.62 | 300 | 7.7 | 0.9 |
| 2-29 | 32 | 5 | 137 | 63.1 | 1,707 | 60 | 3,888 | 7.29 | 473 | 12.2 | 0.6 |
| 3-29 | 36 | 5 | 140 | 64.5 | 1,957 | 60 | 3,888 | 6.15 | 399 | 10.3 | 0.3 |
| 12-29 | 30 | 5 | 133 | 61.3 | 1,357 | 60 | 3,888 | 6.71 | 435 | 11.2 | ... |

TABLE 3.—*Morphine Recovered in Urine Following Abrupt Withdrawal of the Drug*

| Case | 0-2 Hours, Mg. | 2-4 Hours, Mg. | 4-6 Hours, Mg. | 6-8 Hours, Mg. | 8-10 Hours, Mg. | 10-12 Hours, Mg. | 12-16 Hours, Mg. | 16-20 Hours, Mg. | 20-24 Hours, Mg. | 24-30 Hours, Mg. |
|---|---|---|---|---|---|---|---|---|---|---|
| 9-29* | 40.1 | 11.5 | 9.6 | 8.5 | 6.6 | 4.9 | 5.6 | 5.0 | 4.0 | 11.2 |
| 6-29* | 26.7 | 11.2 | 9.0 | 5.6 | 5.5 | 3.5 | 6.7 | 3.3 | 4.2 | 6.8 |

* Received 30 grains (1.944 Gm.) of morphine sulphate daily, 5 grains (0.324 Gm.) at four hour intervals. The last injection was given at 9 a. m. The six hour period immediately following readministration of 5 grains (0.324 Gm.) of morphine sulphate resulted in a recovery of 49.6 mg. in case 9-29, and in a recovery of 52.1 mg. in case 6-29.

The rate of elimination of morphine in the urine following the abrupt withdrawal in the two cases represented in both table 3 and chart 1 showed a rapid fall during the first four hours, after which a more constant level was maintained.

The rapid decrease in excretion during the first four hours was also noted in short period experiments for six hours following a dose of 5 grains of morphine sulphate. The morphine eliminated during the first two hours was three times that eliminated during the fifth and sixth hours. During withdrawal, the patient in case 9-29 eliminated 0.051 Gm., or slightly less than a grain, in the first four hours, 0.15 Gm. for the four to eight hour interval, or slightly more than

one-fourth grain, and then an hourly average of about a thirtieth of a grain during the rest of the experiment. During withdrawal, the patient in case 6-29 eliminated about 0.040 Gm. the first four hours or a little less than two thirds of a grain, one-fourth grain for the next four hours, and an hourly average of a fortieth of a grain for the rest of the experiment. Both addicts had been receiving 5 grains every four hours and, each time the administration was due, showed the usual eagerness for the drug. When the interval was lengthened to eight hours, restlessness manifested itself and a dosage of one-fourth grain given at this time had little effect. These curves, we think, show clearly a relationship between the rapidity of excretion of morphine and the desire for the next dose. As the total amount of drug in the body falls to a certain level, indicated by the change of rate of excretion about

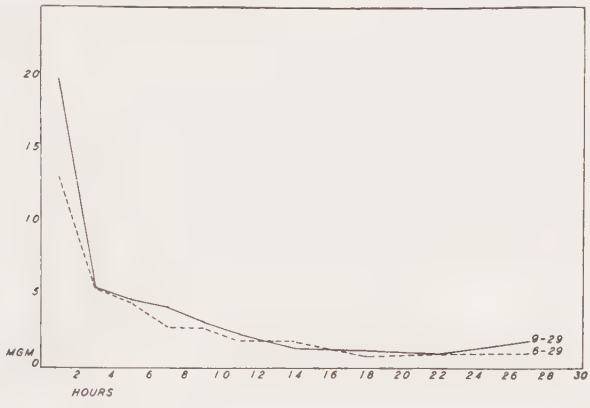


Chart 1.—Curve of morphine excretion in the urine (cases 9-29 and 6-29) at two hour intervals following abrupt withdrawal of the drug for thirty hours. The total amount of morphine given twenty-four hours prior to withdrawal was 30 grains (1.944 Gm.). The last single dose was 5 grains (0.324 Gm.).

the fifth hour, the patient shows an eagerness for the drug. If no drug is given at this time and that present in the body is further depleted, symptoms of withdrawal soon become evident.

Chart 2 contains the record of the temperature of the patient with pneumonia (case 11-29), as well as of the elimination of morphine during the various arbitrary periods and the total nitrogen during these same periods. Throughout the entire course of the disease and convalescence, he received 15 grains every twenty-four hour period. It will be noted that during the first three days of fever the patient eliminated in the urine 13.3 per cent of the total morphine given. Following the first three days of the fever the patient became desperately ill, and continued so for four days; during this time the elimination of morphine in the urine was 18.2 per cent of the amount administered. The crisis

now ensued and during the following forty-eight hours only 15.7 per cent of the morphine appeared in the urine. A week later, during what we term the convalescent period, 13 per cent of the morphine given was recovered, and two weeks after the crisis the amount eliminated was still the same.

It is during the period just preceding the crisis in pneumonia that the various organs began to show cloudy swelling and degenerative processes; the urine in this case, however, remained remarkably free from albumin. During this period the total excretion of nitrogen as well as the elimination of morphine rose. This relationship is striking. Increased elimination of nitrogen indicates a break-down of the tissues,

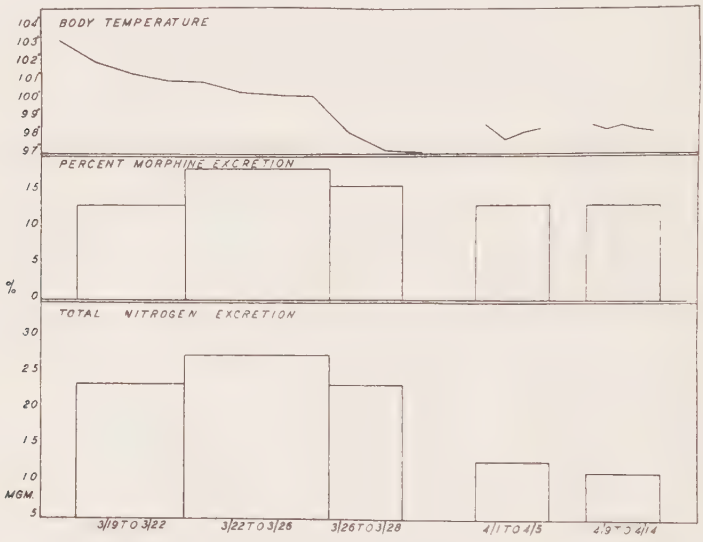


Chart 2.—Curve showing the bodily temperature and the excretion of morphine and total nitrogen in the urine per twenty-four hour period during the illness and convalescence of a human addict suffering with pneumonia. Fifteen grains of morphine was administered daily throughout the disease and convalescence.

while increased elimination of morphine probably indicates a decreased capacity for retaining or destroying the drug. Hence, as those tissues which normally retain or destroy morphine begin to degenerate, the kidneys eliminate the excess drug.

The prompt recovery of the addict while receiving the 15 grains daily throughout the period of illness and convalescence supports the belief in the harmlessness of the drug on organic functions when the body is accustomed to it. This statement may be challenged in this particular case and the question may be raised whether the patient might not have been less ill had he not been given the drug. However, realiz-

ing that withholding the drug from an addict always results in the appearance of symptoms of withdrawal and not wishing to add to the patient's suffering, we felt justified in continuing the drug to avoid the discomfort of withdrawal.

The general condition of the healthy addicts under these various dosages is of interest. It was not a difficult procedure to increase the dosage from 10 (0.648 Gm.) to 60 grains daily within two or three days. Practically all our patients showed a gain in weight in the hospital while receiving these various amounts. No symptoms of intoxication appeared during the administration of the large quantities. One patient showed a tendency to slight drowsiness when left absolutely alone, but any interesting event or conversation resulted in his immediate attention and participation. Sudden reduction from 60 to 30 grains resulted in a marked change of disposition; this was more marked in abrupt reduction from 30 to 15 grains, and was even worse in reduction from 15 to 7½ grains (0.486 Gm.). All patients subjected to this drastic reduction manifested marked changes in disposition. No symptoms of withdrawal were evident, except slight relief from constipation. The patients complained bitterly during this abrupt reduction, but we are convinced that this would have been avoided had not a certain familiarity developed between the patients and the observers during the progress of the experiment.

## CONCLUSIONS

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. The daily administration of 15, 30 and 60 grains resulted in an average elimination of 8.7, 9.8 and 10.7 per cent, respectively. The length of addiction, quantities taken just prior to admission, age, weight and volume of urine did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions.

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours, followed by a much lower and constant level for the next twenty-six hours.

The elimination of morphine in an addict suffering with lobar pneumonia, to whom 15 grains was administered daily throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when he was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine.

## XI. GENERAL SUMMARY

The narcotic problem is recognized today as one of the most important medical and sociologic problems confronting the medical profession. Although isolated studies on the problem have been made from time to time, no comprehensive investigation of its aspects, biologic, medical, social, economic and legal, has been consistently pursued until recent years. The Committee on Drug Addiction in affiliation with the Bureau of Social Hygiene, Inc., of New York has been engaged since 1921 in the study of this important problem. An extensive compilation of facts known and of views held with respect to opium addiction was made by Terry and Pellens [1] and published by the committee in book form. These inquiries demonstrated an urgent need for further investigation of the various phases of the problem by careful scientific methods, and accordingly the committee subsidized a number of field studies, experimentation in several university laboratories and a clinical study of the addict in the wards of the Philadelphia General Hospital.

The results of this clinical study have been published in a series of papers of which this is a brief summary.

The study was designed to determine whether objective investigations would reveal any changes that can be measured by physical, chemical or physiologic methods in the addict who is taking daily doses of from ½ to 60 grains (0.032 to 3.94 Gm.) of heroin or morphine that would differentiate him from a normal person, would serve to identify the state of opium addiction or would provide indications to guide in his rehabilitation.

It aimed furthermore to study by similar methods the addict during the period immediately after withdrawal of the drug at the time when he is suffering from "withdrawal symptoms." This characteristic train of symptoms consists, in about the following order, of yawning, lacrimation, sneezing, restlessness, sweating, hot flashes and chills, vomiting, diarrhea, cramps in the extremities and abdomen, muscular tremors, marked irritability, complaints of extreme weakness, loss of weight, marked pilomotor activity, rarely diplopia and occasionally death. These symptoms reach their height at the end of about seventy-two hours following the withdrawal of the drug, and with the exception of occasional complaints of weakness, gradually subside in from five days to two weeks. Readministration of morphine in the amounts usually taken or in smaller amounts will within from five to thirty minutes bring about

1. Terry, Charles E., and Pellens, Mildred: The Opium Problem, Camden, N. J., Haddon Craftsmen, 1925.

complete relief from all these symptoms. The addict professes to feel normal again with regained strength.

After successful withdrawal when the drug has been withheld for from ten days to two weeks the addict is taking food normally, has regained his weight and presents the picture of well being. If he should now revert to the drug, he will never start with more than 1/8 or 1/4 grain (0.008 or 0.016 Gm.) of heroin or morphine, larger amounts than this causing toxic symptoms and even death. The addict is again for the time being similar to normal persons in respect to tolerance. A group of addicts at this period was studied by the same methods to detect any difference in them when their tolerance had disappeared.

Finally a study was made in collaboration with the Department of Pharmacology of the University of Pennsylvania on the excretion of morphine in the addict.

Our general method of approach in these studies has been as follows. A suitable addict having been selected on admission, his dosage of morphine was for a time continued hypodermatically in sufficient quantities to prevent the appearance of withdrawal symptoms. During this period of several days he was measured, weighed, his vital capacity was determined and he was allowed to remain about the ward. A standard series of studies was then carried out and designated as "during the addiction period." The drug was then abruptly withdrawn for forty-eight hours, the patient being carefully watched and observed during this period. At the end of this time, the same series of studies was again made. He was now given sufficient morphine to bring about complete relief. Again the same studies were carried out. Within a day or two the hyoscine method of treatment was employed, and at the end of about ten days when the patient was ready for discharge from the hospital and said that he was feeling well, the series of studies was again carried out.

Our investigations were readily made during addiction and following treatment but met with many failures during withdrawal, as the patients often refused to cooperate. In the first paper of the series, we have described the type of addict with which we have dealt and have pointed out some of the precautions which must be observed to avoid being deceived by the addict's tricks to obtain drug and by his tendency to simulate a state of either suffering or of well being as may best serve his purposes.

## RESULTS OF STUDIES

The results may be summarized as follows:

In a series of opium addicts who were given morphine in sufficient quantities to prevent withdrawal symptoms, a study of the pulse rate and blood pressure while the subjects were standing and again while

they were reclining, of the respiration, electrocardiograms and the response to staircase climbing tests, resulted in the finding of no marked deviation in the behavior of the circulation and respiration from that of normal persons.

In 70 per cent of the cases the average pulse rate while the subject was reclining was slightly below the usual average figures given for normal persons.

Orthodiagramatic measurements showed a tendency to a smaller size for the heart than the average for normal persons.[2]

A series of addicts receiving morphine sulphate hypodermatically has been studied with respect to the following: hemoglobin, red blood cell count, white blood cell count, differential count, sedimentation rate, blood viscosity, cell volume, Wassermann reaction, specific gravity of the blood and plasma, plasma refractive index, dry matter of the blood and plasma, plasma $p_H$, carbon dioxide capacity of the plasma, serum conductivity, sugar, urea, creatinine, uric acid, cholesterol, chloride and lactic acid of the blood and calcium, magnesium and phosphate of the serum.

In a general way there was a tendency for low red count, and high leukocyte count, but not uniformly in all cases. The cholesterol was usually increased and the phosphate diminished. The lactic acid was uniformly high. No other constituents showed any suggestive departure from the normal.

A slight degree of anemia may be present when the addict is forced to live in poor hygienic surroundings when all his funds are required to purchase the drug at the expense of sufficient nourishing foods.[3]

Studies of the stomach, kidney, liver, basal metabolism, thymus, temperature, dextrose response to epinephrine and to morphine revealed no fundamental differences in addicts who were administered morphine to supply their needs, except a slight delay in the average response of gastric secretion to a test meal, the presence of albumin in the urine in 17 per cent of the cases and wide fluctuations of the individual determinations of basal metabolism but an average metabolism within the normal limits. A delay in the return to normal of the blood sugar following the ingestion of dextrose by mouth was also noted.[4]

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2. III: The Circulation and Respiration of Human Addicts During the Administration of Morphine, p. 21.

3. IV: The Blood of the Human Addict During the Administration of Morphine, p. 33.

4. V: Miscellaneous Observations on Human Addicts During the Administration of Morphine, p. 40.

We have been unable to detect any marked physical deterioration or impairment of physical fitness aside from the addiction per se in the series of cases of opium addiction studied during the administration of morphine.

The existence of considerable emaciation in certain cases we believe to be caused by the unhygienic and impoverished life of the addict rather than by the direct effects of the drug.[5]

Abrupt withdrawal of morphine for twenty-four hours in four addicts resulted in the appearance of mild withdrawal symptoms. These symptoms were accompanied with slight negligible changes in the pulse rate, leukocyte count and basal metabolism rate. Changes in behavior and irritability would indicate that mental suffering begins before physical suffering.

Abrupt withdrawal of morphine for forty-eight hours from a series of ten addicts resulted in the appearance of rather severe withdrawal symptoms. One addict showed diplopia. These changes were accompanied by a definite leukocytosis in eight of the ten cases, concentration of the blood in all cases and a slight rise in cholesterol of the blood in seven. Albuminuria was found in two cases. The $p_H$ of the blood, urea nitrogen and sugar showed no changes. Considerable loss of weight was found during the forty-eight hour withdrawal period.

Following the readministration of the drug and relief from subjective symptoms, the increased leukocyte count and concentration of the blood still remained, as did the diplopia and muscular twitchings of the face, for several hours. A rise in the percentage saturation of the oxygen of venous blood was noted in all cases following the readministration of the morphine. The circulatory changes noted were a slight increase in the pulse rate and a slight fall in systolic pressure. Staircase climbing and Schneider's test showed a decrease in the efficiency of the circulation following the readministration of the drug when compared to the results obtained at the end of the forty-eight hour withdrawal period.[6]

Abrupt withdrawal of morphine in a series of human opium addicts resulted in a negative water balance, and in two of these subjects in increased elimination of uric acid. The negative water balance is most likely due to failure to take sufficient food and water although increased loss of water from increased metabolism cannot be entirely excluded,

5. II: Physical Characteristics and Physical Fitness of Addicts During the Administration of Morphine, p. 13.

6. VI: The Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts, with Special Reference to the Composition of the Blood, the Circulation and the Metabolism, p. 51.

particularly in view of the restlessness of these subjects during withdrawal.

While taking their first year final examinations, three medical students used as control subjects failed to show a negative water balance, any increase in frequency of urination or increased twenty-four hour output, and retained their weights, on the days of the final examinations.[7]

Studies of a series of opium addicts before and after treatment with scopolamine resulted in the following positive changes: loss of weight, slight rise in temperature, appearance of albuminuria, slight leukocytosis, slight concentration of the blood, a rise in the $p_H$ of the blood, a rise in the lactic acid of the blood, a fall in the carbon dioxide capacity and a fall in the total number of points scored with Schneider's test of physical fitness.

No significant changes were found in a comparison of the pulse, respiration rates and blood pressure while the addict was reclining, heart measurements, electrocardiographic studies, staircase climbing tests, effect of atropine sulphate on the P-R interval, vital capacities, blood urea nitrogen, blood sugar, blood uric acid, blood cholesterol, whole blood chloride, serum calcium and phosphate, blood viscosity, sedimentation tests, basal metabolism, phenolsulphonphthalein tests, phenoltetrachlorphthalein test of liver function, icterus index, van den Bergh's tests and blood sugar response to epinephrine.

The few positive observations do not coincide with the general appearance and behavior of the addict. He may present some or all of the foregoing positive observations and yet appear and behave as though he were normal. On the other hand, he may give the appearance of one who is quite ill and yet not show any of the foregoing positive observations.[8]

The effect of intramuscular and intravenous administration of large doses of morphine was tested on five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four, accustomed to the hypodermatic method, volunteered as subjects for this study.

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignifi-

7. IX: Water Balance Studies During the Administration and Withdrawal of Morphine, p. 96.

8. VII: A Comprehensive Study of Effects of the Scopolamine Treatment for Morphine Addiction, p. 67.

cant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood and the behavior of the addict.

The intravenous administration of 20 and 11 grains (1.3 and 0.715 Gm.) to two addicts following a forty-eight hour withdrawal period in fifty-six minutes and one hour and sixteen minutes, respectively, also failed to produce any significant physiologic changes or changes in behavior.

Analyses of the blood for morphine showed the presence of less than 1 mg. per twenty-five cubic centimeters of blood, indicating its rapid removal following the completion of the injection.[9]

In a series of addicts it has been possible to control reliably the morphine dosage, to vary this at will and to collect the excreta quantitatively.

Quantitative estimation of the elimination of morphine in the urine of human addicts showed a remarkable constancy in ratio to the amounts administered. Daily administration of 15 (0.972 Gm.), 30 (1.945 Gm.) and 60 grains (3.888 Gm.) resulted in an average percentage elimination of 8.7, 9.8 and 10.7, respectively. The length of addiction, quantities taken just prior to admission, age, weight and urine volume did not influence this rate.

Fecal excretion of morphine fell far below the urinary level, but was too variable to justify general conclusions.

Abrupt withdrawal of morphine resulted in a rapid fall in urinary excretion during the first four hours followed by a much lower and constant level for the next twenty-six hours.

The elimination of morphine in an addict suffering with lobar pneumonia, to whom a daily administration of 15 grains (0.972 Gm.) was maintained throughout the illness and convalescence, showed the same level of excretion during the early part of the disease, following the crisis and during the convalescent period, but a rise in the period just before the crisis when the patient was critically ill. No unusual signs or symptoms appeared during the illness that could be attributed to the morphine.[10]

COMMENT

These results are of definite importance. The study shows that morphine addiction is not characterized by physical deterioration or impairment of physical fitness aside from the addiction per se. There

9. VIII: The Effects of Intramuscular and Intravenous Administration of Large Doses of Morphine to Human Addicts, p. 77.

10. X: The Excretion of Morphine by Human Addicts, p. 103.

is no evidence of change in the circulatory, hepatic, renal or endocrine functions. When it is considered that these subjects had been addicted for at least five years, some of them for as long as twenty years, these negative observations are highly significant. The study offers substantial grounds for the belief that were it possible to relieve the addict of his addiction complete rehabilitation could be expected.

The abrupt withdrawal of morphine was accompanied by only slight changes in the physiologic mechanisms studied, changes which afforded no adequate explanation of the withdrawal symptoms.

The readministration of morphine during the period of the withdrawal symptoms was not accompanied by return to normal of those few positive observations characteristic of the withdrawal period in spite of the apparent return of the addicts to a sense of well being. Schneider's test of physical fitness and the staircase climbing test indicated a poorer response than during the period of suffering.

Following treatment and just before discharge from the hospital, our studies again indicate few changes except that the average leukocyte count was still high, a slight concentration of the blood still persisted, a slight rise in the average for the $p_H$ and lactic acid of the plasma and a decided fall in the efficiency tests were found. One cannot correlate these observations with the behavior of the patients.

The study appears to us to be conclusive with respect to the physiologic reactions of the addict which we investigated. It indicates, however, the necessity for a study of the addict from some new standpoint in order to reveal the factors which induce and maintain the state of addiction and which on abrupt withdrawal of the drug elicit the withdrawal symptoms.

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